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The cardiovascular profile and dietary intake of post-cardiac transplant patients

Melinda Morrison
University of Wollongong

THE CARDIOVASCULAR PROFILE AND DIETARY INTAKE OF POST-CARDIAC TRANSPLANT PATIENTS

By
Melinda Morrison

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ABSTRACT

Advanced coronary artery disease (CAD) is the most frequently observed long term complication of cardiac transplantation. Studies report prevalence rates up to 70 per cent at five years post-transplant. In addition to immunologically mediated factors, conventional cardiovascular risk factors have been implicated in the development of CAD. The purpose of this research project was to investigate the cardiovascular profile and dietary intake of cardiac transplant recipients at twelve to twenty-four months post-transplant at St. Vincent's Hospital, Sydney.

The study population consisted of 27 post-cardiac transplant patients. Data including body weight, serum lipid levels, blood pressure and the presence of diabetes mellitus in the post-transplant period was retrospectively analysed from St. Vincent's Hospital records. Waist-to-hip ratios (WHR) were measured at the time of participation in the study and compared to recommendations. Each participant was also interviewed for approximately one hour to obtain an extensive diet history.

Analysis of anthropometric data indicated that body weight increased progressively throughout the post-transplant period. At twelve months post-transplant, 56 per cent of recipients were classified as overweight and one third of these obese. Mean weight gain was 7.8 kg. Eighty eight per cent of the transplant population displayed WHR's larger than desirable. Cholesterol levels showed a steady post-transplant increase which reached statistical significance at three months post-transplant ($p<0.01$). Hypertension, as indicated by a diastolic blood pressure >95 mmHg or the administration of anti-hypertensive medications was present in 73 per cent of this population at 12 months post-operative. However, none of the participants displayed persistent uncontrolled hypertension. Post-transplant diabetes mellitus was prevalent in 19 per cent of transplant recipients. An analysis of dietary intake data indicated that 63 per cent of transplant recipients had a fat intake greater

than recommended, with a mean 31.7 per cent contribution to energy. Sodium and saturated fat intakes were also significantly greater than current healthy heart recommendations ($p<0.01$; $p<0.05$).

The findings of this study suggest that cardiovascular risk factors are frequent in long term cardiac transplant recipients. Biochemical indicators and body weight should therefore be regularly monitored throughout the post-transplant period. Whilst more stringent efforts at weight control including intensive dietary intervention and encouragement of exercise within the first 12 months post-transplant, may be beneficial in improving cardiovascular profile and possibly assist in the prevention of cardiovascular complications such as CAD.

2. Literature Review

1. INTRODUCTION

Cardiac transplant recipients are a high risk group for the development of long term cardiovascular complications including coronary artery disease. The aetiology of this disorder remains highly controversial, however conventional cardiovascular risk factors including hyperlipidaemia, obesity, hypertension, diabetes mellitus and dietary intake have been suggested to play a role.

Anecdotal evidence from the St. Vincent's Hospital cardiac transplant population suggests that cardiovascular risk factors are prevalent in a large proportion of transplant recipients. Information regarding the profile of these risk factors and the long term dietary intake of this population, however, is largely unreported in Australia. This study attempts to address these issues by determining the long term cardiovascular profile and nutritional status of this group. In turn, this information will form the basis for an evaluation of the effectiveness of current nutrition services at St. Vincent's Hospital, Sydney.

1.1 Aim

The aim of this project is to investigate the cardiovascular profile and dietary intake of St. Vincent's Hospital cardiac transplant patients at twelve to twenty-four months post-transplant.

1.2 Objectives

The objectives of this project include:

1.2.1 To record blood lipid levels in cardiac transplant recipients and determine changes in lipid profile in the post-transplant period

1.4.2 To record body weight in cardiac transplant recipients and determine the pattern of weight change in the post-transplant period

1.4.3 To determine the body fat distribution of cardiac transplant recipients in the post-transplant period

1.2.4 To determine what proportion of cardiac transplant recipients display diabetes mellitus in the post-transplant period

1.2.5 To determine what proportion of cardiac transplant recipients display hypertension in the post-transplant period

1.2.6 To describe the usual dietary intake of cardiac transplant recipients in the post-transplant period and compare with current dietary recommendations

1.3 Definition of Terms

Cardiomyopathy:

A disease of the muscle of the heart. Can be dilated, hypertrophic or restrictive in its presentation. Can be idiopathic - of unknown cause or related to the outcome a variety of factors (eg. alcohol) (Weatherall et al 1989)

Cardiovascular Risk Factors:

Factors which have been identified as increasing the risk of coronary heart disease. Includes high blood pressure, obesity, elevated cholesterol, diabetes mellitus, diet, smoking and physical inactivity (National Heart Foundation 1989).

Congestive Cardiac Failure:

A disorder where the heart fails to adequately pump blood throughout the body. The result is circulatory congestion and sodium retention which leads to shortness of breath and oedema (Rothenberg and Chapman 1994).

Coronary Artery Disease (CAD) :

A disorder whereby lipid filled plaques develop on the inner walls of the coronary arteries narrowing the lumen and reducing blood flow to the heart. Also known as atherosclerosis (Rothenberg and Chapman 1994).

Hyperlipidaemia:

Elevated levels of lipids in the blood. These include cholesterol, lipoprotein subfractions (low density lipoprotein, high density lipoprotein) and triglycerides.

Hypercholesterolaemia:

Serum cholesterol levels exceeding 5.5 mmol / Litre (National Heart Foundation 1989)

Hypertriglyceridaemia:

Serum triglyceride levels exceeding 1.8 mmol / Litre (Curtin University of Technology 1992)

Hypertension:

Blood pressure elevated above diastole 95mmHg and systole 150mmHg (Stamler et al 1993). Although a variety of definitions are used by different researchers.

Immunosuppressants:

Medications which act to suppress normal immune responses. In heart transplant patients these commonly include corticosteroids, cyclosporine and azathioprine (Reynolds 1989).

Ischaemic Heart Disease (IHD):

A disease whereby there is a decreased blood flow to the heart. Usually the result of atherosclerosis (Rothenberg and Chapman 1994).

Myocarditis:

Inflammation of the myocardium (heart muscle). Can be caused by viral infections, or bacteria, results in fatigue, dyspnoea and tachycardia (Weatherall et al 1989).

Orthotopic Heart / Cardiac Transplantation:

A medical procedure whereby the heart from a *donor* operatively replaces a *recipients* own failed heart.

Peripartum Heart Disease:

Dilated cardiomyopathy with pregnancy acting as a facilitator (Weatherall et al 1989).

2.1 CORONARY ARTERY DISEASE IN CARDIAC TRANSPLANTATION

Cardiac transplantation has become recognised as a successful treatment for end stage heart failure. Each year over 100 orthotopic heart transplants are performed in Australia and to date over 800 transplants have been completed among the four major transplant centres. The major indications for cardiac transplantation include ischaemic heart disease, idiopathic cardiomyopathy, myocarditis and congenital heart disease. Survival rates for transplant recipients have improved significantly over the past two decades, reaching 86 per cent at one year and approximately 78 per cent at five years (Australian & New Zealand Cardiothoracic Organ Transplant Registry 1994). Mortality during the first year is related to operative complications, infection and rejection (Mann 1992). However, the most frequently observed long term complication of cardiac transplantation is an accelerated form of coronary artery disease (CAD) (Scott and Dark 1992).

The clinical presentation of post-transplant CAD often differs from conventional atherosclerosis. It frequently develops in smaller coronary vessels, is concentric, diffuse and characteristically occurs at a rapid rate without the development of a collateral blood supply (Mullins et al 1992). Less commonly, transplant CAD may appear as a plaque which is indistinguishable from conventional atherosclerosis (Schroeder et al 1992). Transplant CAD is often clinically silent in its development, as a result of denervation (Gao et al 1990). Mortality due to CAD is commonly the result of fatal myocardial infarcts, congestive heart failure and cardiac arrhythmia's. In addition, graft failure as a result of CAD is a frequent indication for re-transplantation (Schroeder et al 1992).

Prevalence rates for post-transplant CAD have been reported from two to 28 per cent at one year post-transplant and up to 70 per cent at five years (Gao et al 1989, Narrod et al 1989, Mullins et al 1992). Survival rates appear to be a function of CAD advancement. Mullins et al (1992) reported a 60 to 80 per cent survival rate three years after CAD

diagnosis. However, survival rates in more advanced CAD are much poorer. Three year survival rates of 22 per cent have been reported for CAD affecting a single vessel with greater than 40 per cent stenoses, whilst survival with triple vessel disease over the same period is as low as 6 per cent (Keogh et al 1991).

A number of factors have been suggested to predispose the heart transplant recipient to CAD, although the relative contribution of each has not been established. It has been suggested that post-transplant CAD is an immunological mediated disease (Stovin et al 1991). It has been related to donor specific cytotoxic antibodies and cellular rejection. Uretsky et al (1987) in studies on CAD, reported that transplant recipients with more than two episodes of rejection within the first year post-transplant, had an increased risk of developing CAD. However, these findings have not been consistently reported in the literature (Stovin et al 1991).

Viral infections, notably cytomegalovirus (CMV) have been shown to correlate with the development of post-transplant CAD (Stovin et al 1991). CMV has been reported in up to 90 per cent of heart transplant recipients (Dummer 1990). It has been suggested that CMV may be an initiator of atherosclerosis through its damaging influence on the endothelium (Stovin et al 1991). In animal studies, the virus has been shown to increase cholesterol incorporation into the arterial intima and alter the normal synthesis and metabolism of cholesterol (Miller 1991). Studies on the influence of CMV have produced mixed results with some reporting a relationship (Stovin et al 1991) and others finding no significant influence on CAD development (Sharples et al 1991).

Donor and recipient characteristics have both been suggested to play a role in post-transplant CAD. A number of studies have indicated that CAD occurs more commonly in recipients of hearts from older donors (Sharples et al 1991). Older recipients themselves, notably over the age of 50 years, may also be at greater risk of post-transplant CAD. The sex of both donor and recipient may additionally influence CAD development (Sharples et

al 1991), as might donor ischaemic time (Miller 1991). Further, certain tissue type mismatches may be predictive of CAD development (Stovin et al 1991).

There is some evidence that pre-operative diagnosis may be related to CAD development. Transplant recipients with ischaemic heart disease as the initial cause of heart failure, have been shown in some studies to be at an increased risk of developing this accelerated form of CAD (Sharples et al 1991). In comparison recipients with a diagnosed cardiovascular disease without atherosclerotic involvement, such as a cardiomyopathy or valvular disease may be at lower risk. Again, this is controversial in the literature.

A relationship between immunosuppressive medications including cyclosporine and corticosteroids and CAD has been suggested. It is thought that prolonged treatment with these medications may directly damage graft vessels (Dummer 1990). Indirect effects such as hyperlipidaemia, hypertension and glucose intolerance have also been demonstrated.

Conventional cardiovascular risk factors including hyperlipidaema, diabetes mellitus, obesity and diet have also been implicated in this disorder. Due to the multi-factorial nature of post-transplant CAD however, the role of these risk factors has not been delineated. Eich et al (1990) proposed that the combined effect of endothelial damage and associated risk factors may play a key role in post-transplant CAD. In this model, immunosuppressive medications, immune responses, and viral infections combined with diabetes mellitus and dyslipidaemia result in damage to the endothelium, platelet aggregation, intimal smooth muscle proliferation and consequent CAD (refer to Figure one). The aetiology, significance and role of these conventional risk factors in post transplant CAD will be reviewed in each of the chapters to follow.

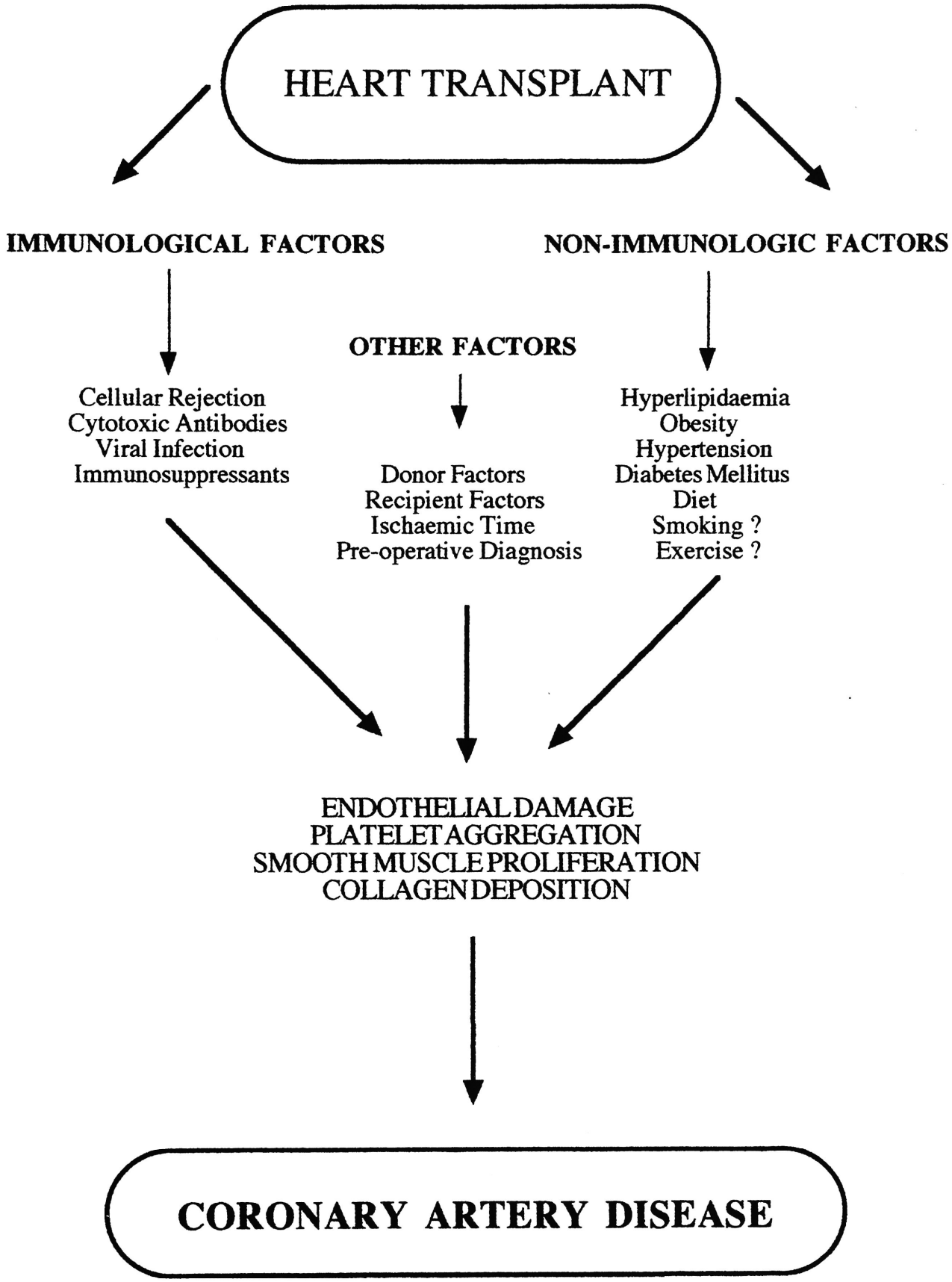


Figure 2.1.1 Predisposing factors to the development of CAD in cardiac transplant recipients (Adapted from Eich et al (1990))

2.2 HYPERLIPIDAEMIA

2.2.1. Hyperlipidaemia in Coronary Heart Disease

Raised plasma lipids have been clearly established as a strong and independent risk factor for the development of coronary heart disease in the general population. Hyperlipidaemia, which includes elevations in total cholesterol, cholesterol sub-fractions and triglyceride levels, increases cardiovascular risk through its influence on the development of atherosclerosis (Gotto et al 1990).

In the general population, the risk of heart disease begins to increase at total plasma cholesterol levels above 3.9 mmol/L. The most considerable risk, however, occurs at cholesterol levels in excess of 5.2 mmol/L (Keogh 1987). The low density lipoprotein (LDL) sub-fraction of cholesterol poses a significantly increased risk as a result of its atherogenicity. High density lipoprotein (HDL) cholesterol on the other hand has been shown to have a protective effect on cardiovascular health (Romm et al 1991). Further, plasma triglycerides have been identified as a risk factor for CHD. However, this risk is thought to be influenced by the association of hypertriglyceridaemia with low HDL cholesterol, obesity and insulin resistance. It appears that elevated triglycerides pose cardiovascular risk when HDL cholesterol is depressed in the presence of elevated total cholesterol (Castelli 1986).

The role of hyperlipidaemia in coronary heart disease has been consistently reported in both epidemiological and clinical studies. The *Multiple Risk Factor Intervention Trial*, a randomised primary prevention study, for example, provided epidemiological data to suggest that mortality from heart disease was strongly associated with serum cholesterol levels (Multiple Risk Factor Intervention Trial Research Group 1982). Similarly, other studies such as those from *Framingham* and the *Lipid Research Clinics* have reported

comparable evidence for the adverse cardiovascular consequences of hyperlipidaemia (Kannel et al 1971; Lipid Research Clinics Program 1984).

2.2.2 Cardiac Transplant Hyperlipidaemia

Considering the evidence supporting a link between elevated blood lipids and heart disease, it is possible that hyperlipidaemia plays a role in the establishment of post-transplant CAD. Studies by Eich et al (1991) support this hypothesis. In a retrospective review of 38 heart transplant recipients, they found that hypercholesterolaemia at six months post-transplant was a strong predictor of subsequent CAD. Similarly, Barbir et al (1991), in comparing cumulative cardiovascular risk in patients with and without hyperlipidaemia, indicated that the probability of CAD was greater in transplant recipients with cholesterol above 5.8 mmol/L. In the same study, the incidence of CAD was greater in patients with triglyceride levels above 1.4 mmol/L. Another study by Winters et al (1990), also confirmed a significant relationship. In an analysis of the extent of coronary arteriopathy in transplant recipients, they reported that patients with higher mean cholesterol and triglyceride levels had a significantly more luminal narrowing. These results and those from a number of other studies clearly suggest a role for hyperlipidaemia in the evolution of CAD. However, some researchers have suggested that hyperlipidaemia occurring in combination with other factors such as cytotoxic antibodies and HLA mismatch is necessary for the development of CAD in this setting (Ballantyne et al 1987).

Hyperlipidaemia is frequently demonstrated in both renal and heart transplant recipients. The incidence in heart transplant patients has been reported to vary from 33 to 83 per cent for hypercholesterolaemia (Keogh et al 1988; Rudas et al 1990). Hypertriglyceridaemia has been found in up to 10 per cent of the same population (Keogh et al 1988). There is considerable variability in the literature regarding the predominate lipid abnormalities. Grady and Herold (1988) found that elevations in post-transplant triglyceride and total cholesterol were most frequent. They reported an increase in mean triglyceride

concentrations from 3.5 to 5.7 mmol/L. Whilst total cholesterol increased from 4.6 to 6.8 mmol/L. Keogh et al (1988) confirmed similar increases in total cholesterol, however, changes in triglycerides were less frequent. Elevations in lipid sub-fractions have also been reported. Becker et al (1988) in a study of recipients from a number of heart transplant centres, discovered elevations in LDL and HDL cholesterol as well as total cholesterol and triglyceride levels. Thirty eight per cent of these patients were above the 90th percentile for total cholesterol when compared to a reference population, indicating that hyperlipidaemia is a particular concern for this population.

In heart transplant recipients, hyperlipidaemia appears to occur as a progressive increase in lipid levels within the first twelve months post-transplant. Although this pattern has shown variation in different studies. Keogh et al (1988) in a study on twenty-two heart transplant recipients reported mean serum cholesterol increases which peaked at 3 months post-transplant. At twelve months post-transplant a significant degree of hypercholesterolaemia (> 6.5 mmol/L) was found in nine of the transplant patients. Mean serum triglyceride levels were also found to be higher in the post-transplant period. Similarly, Ballantyne et al (1992) in a larger study, reported elevated total cholesterol and triglycerides in the first three months following transplantation. They found no significant changes in lipid profile after this time. The findings of Lake et al (1993) however, propose a different pattern of hyperlipidaemia. In a prospective study of 89 transplant recipients, they noted increases in total cholesterol, LDL cholesterol and blood triglycerides at 12 months, which remained elevated at 24 months post-transplant. Earlier post-operative elevations in lipids have also been suggested by some researchers. Stamler et al (1988), for example, reported significant elevations in both LDL and total cholesterol at 2 weeks post-transplant. At 3 months, these levels peaked and remained elevated for 12 months post-operatively. In the same study triglyceride and HDL elevations were noted at 3 months post-transplant but did not reach statistical significance.

Overall, the majority of studies report evidence of hyperlipidaemia in cardiac transplant recipients. Although inconsistencies in the literature are evident, it is important to recognise that there are a number of potential sources of inaccuracy in determining blood lipid levels. In the pre-transplant period, patients are susceptible to cardiac cachexia, liver dysfunction and in some cases myocardial infarcts, all of which are known to modify serum lipids. Similarly, blood samples taken immediately post-operatively may not reflect true lipid values due to the metabolic stresses of major surgery (Rosenson 1993; Ballantyne et al 1987). Hence data which suggests changes in lipid profiles from pre to post-transplant must be interpreted with care. Further, drawing comparisons between studies is difficult with different variables, for example, medication protocols potentially affecting lipid levels.

The mechanism by which hyperlipidaemia develops in the post-transplant period is not clear, but immunosuppressive treatment has been implicated as a major cause. The negative effects of corticosteroids on lipid levels have been widely reported in patients receiving long-term immunosuppression for inflammatory and connective tissue disorders (Bagdale et al 1970; El-Shaboury and Hayes 1973). In a healthy population, the steroid prednisone has been shown to induce elevations in plasma total cholesterol, LDL cholesterol and HDL cholesterol within 48 hours of administration (Zimmerman et al 1984). More recently similar findings have been reported in heart transplant recipients. The most convincing evidence comes from studies which suggest that cholesterol levels decrease when patients are tapered off steroids. For example, Renuld et al (1989) found that withdrawal of the corticosteroid, prednisone was associated with cholesterol levels of 21 to 26 per cent lower than patients maintained on prednisone therapy. Similar, although less dramatic findings have been reported in other studies (Lake et al 1993). The influence of corticosteroids on blood lipids is thought to occur as a result of decreased post-heparin lipolytic activity, glucose intolerance and increased accumulation of dietary fat (Elasser and von Eickstedt 1992). Although these findings have not been demonstrated in all studies of lipid elevations in transplant patients (Superko et al 1990).

The powerful immunosuppressant, cyclosporine has also been demonstrated to adversely affect lipid profile. Increased levels of total cholesterol and triglycerides have been reported in both renal and heart transplant recipients with cyclosporine administration (Harris et al 1986; Superko et al 1990; Winters et al 1990). Total cholesterol elevations are thought to be the result of increased LDL cholesterol . Whilst cyclosporine has been inversely related to lipoprotein lipase and hence elevated blood triglycerides (Superko et al 1990). Several researchers have reported an adverse effect of cyclosporine on lipid levels. Stamler et al (1988) demonstrated that changes in lipid levels in patients receiving cyclosporine differed from that with other immunosuppressive regimens, an effect which they related to the hepatotoxic effects of this drug. However, failure to control for other variables, including diet and medication makes the significance of these findings questionable. More convincing evidence comes from a trials undertaken by Ballantyne et al (1989). In comparing the lipid profile of patients treated with cyclosporine and those receiving a placebo, they reported significant increases of 21 per cent in total cholesterol and 31 per cent in LDL cholesterol. In comparison, Becker et al (1988), found that the influence of cyclosporine on lipid levels was insignificant. However, they reported that cumulative prednisone exposure was the strongest predictor of unfavourable lipid profiles. Other studies have suggested that cyclosporine therapy enhances the effect of corticosteroids on serum lipids (Johnson 1992). However, there is no clear consensus in the literature regarding the exact role that cyclosporine plays in the establishment of hyperlipidaemia.

Obesity following heart transplantation is a possible contributing factor to the development of lipid abnormalities. Excessive accumulation of body fat, as prevalent in the transplant population has been associated with poor lipid profiles (Bonora et al 1991). A possible role in the development of post-transplant hyperlipidaemia is therefore evident. Studies by Keogh et al (1988) support this suggestion. In research on hyperlipidaemia they demonstrated a correlation between body weight and serum lipid levels. It was suggested that 81 per cent of the variation in total cholesterol and 72 per

cent of that in triglycerides could be explained by increases in body weight. Similarly, Rudas et al (1990) reported that the presence of obesity at one year post-transplant was significantly associated with hyperlipidaemia. Studies on renal transplant recipients have produced similar findings. Vathsala et al (1989) for example, demonstrated that hypertriglyceridaemia in renal transplanted patients was one of several factors aetiologically linked to obesity. Considering the initial cause of weight gain is often corticosteroid related, the development of lipid abnormities via obesity may therefore be a further adverse consequence of steroid administration.

Initial diagnosis and pre-transplant hyperlipidaemia have also been suggested as predictors of lipid profiles following cardiac transplantation. Studies have found that patients with a history of lipid abnormalities show higher post-operative lipid values. Lake et al (1993) reported evidence of this at both 12 and 24 months post-transplant. These findings agree with those of Rudas et al (1990) which suggest that hyperlipidaemia in the post-transplant period results from the normalisation of cardiac function. Elsewhere, a pre-operative diagnosis of coronary artery disease (which is associated with lipid abnormalities) has been reported as being predictive of post-transplant hyperlipidaemia (Rudas et al 1990; Keogh et al 1988; Taylor et al 1989). Although there is considerable support for this relationship it has not been consistently reported in the literature.

As a modifiable cardiovascular risk factor, prevention or effective treatment of hyperlipidaemia would clearly be of some benefit in CAD risk modification. Initial attempts to control lipid elevation through pharmacological lipid lowering agents were largely unsuccessful (Keogh 1987). These medications resulted in a number of adverse side effects and demonstrated little benefit on improving lipid profiles. More recently however, newer treatment protocols have demonstrated improved outcomes. However, potential side effects and drug interactions remain important considerations for these

patients (Ballantyne et al 1989). The efficacy of diet and lifestyle modifications in this setting have been controversial. These will be discussed further in chapters to follow.

In summary, hyperlipidaemia is a significant complication of heart transplantation. Unlike conventional hyperlipidaemia, the aetiology of this disorder has not been established. A multitude of factors have been implicated, yet none has been consistently demonstrated. It is possible that a combination of immunosuppressive medication, obesity, pre-transplant lipid status and pre-operative diagnosis contribute to lipid abnormalities in this setting. Further, renal insufficiency, diabetes, anti-hypertensive medications, recipient age, dietary intake and ethanol may exacerbate changes in lipid profile (Lake et al 1993). Clearly, an effective means of preventing lipid abnormalities would be beneficial to the cardiovascular profile of these patients and possibly alter the pathway for CAD development.

2.3 OBESITY

2.3.1 Obesity and Coronary Heart Disease

Obesity, the excessive accumulation of body fat has been strongly correlated with the development of coronary heart disease. Obese individuals have been reported to have a an increased risk of heart disease, which is associated with considerable morbidity and mortality (Noppa et al 1980). The role of obesity as a cardiovascular risk factor has been shown to be both independent and via the influence on other risk factors (Hubert et al 1983).

The health implications of obesity have been widely reported (Larrson et al 1981; Garrow 1991). Large controlled studies have demonstrated a variety of metabolic and cardiovascular consequences in obese populations. Insulin resistance is one such factor which has been related to the development of diabetes mellitus and poor lipid profiles, hence the risk of coronary heart disease (Hartz et al 1983; Felber 1992). Hypertension has also be reported as a significant complication which may have initiating effects on the process of atherosclerosis (Stamler et al 1978). In addition, abnormalities in serum cholesterol and triglycerides have been demonstrated to occur in obesity (Forde et al 1986; Bonora et al 1991). Further, obesity has been shown to increase cardiac output via its influence on blood volume, stroke volume and left ventricular end-diastolic volume. Hence the consequences may be left ventricular hypertrophy and cardiac failure (Hagan et al 1990). As a result, obesity has negative implications for cardiovascular profile and thus the risk of coronary heart disease.

2.3.2. Body Fat Distribution and Coronary Heart Disease

There is evidence that the distribution of body fat may pose additional cardiovascular risk. Upper body obesity (android) has been more strongly associated with the myriad of metabolic aberrations including hyperinsulinaemia, diabetes mellitus, hypertension and

dyslipidaemia (Egger 1992). In contrast obesity of the lower body (gynoid) has been shown to have fewer health complications (Despres et al 1990). As a result, the android pattern of obesity has been associated with an increased risk of coronary heart disease and consequent morbidity and mortality (Donahue et al 1987; Ducimetiere and Richard 1989; Hartz et al 1990; Rimm et al 1995).

The metabolic consequences of increased adiposity in the upper body region are related to the presence of visceral or intra-abdominal fat (Zamboni et al 1994). As opposed to subcutaneous upper body fat, that of the intra-abdominal region lies deeper within the abdominal cavity and is more metabolically active (Calvert 1991). Consequentially, it influences insulin, glucose, fatty acid and lipoprotein metabolism (Despres et al 1990). Although the mechanisms by which these disturbances occur are not completely understood it is evident that the android pattern of obesity has multiple cardiovascular implications. This is supported by recent research which has described an independent role for central obesity in the development of cardiovascular disease (Hartz et al 1990). However, the fact that abdominal fat increases with age and differs amongst the sexes makes the independent contribution of this pattern of body shape in the absence of obesity per se, controversial. Some researchers have suggested that increased abdominal fat, as indicated by anthropometric measures, enhances the detrimental effects of obesity on metabolism (Depres 1992). Thus an increased body weight in conjunction with a large abdominal region of adiposity may be predictive of cardiovascular risk.

2.3.3 Obesity and Cardiac Transplantation

Excessive weight gain is a frequently observed complication of heart transplantation which has been identified as a prognostic factor in the progression of CAD (Poindexter et al 1990). Prior to transplantation patients may be underweight as a result of compromised cardiac function, suppressed appetite and catabolism. Following transplantation however, significant weight gain often resulting in obesity has been documented in a large proportion of patients (Robert et al 1990).

Obesity is thought to influence the risk of transplant CAD through similar metabolic and cardiovascular pathways as non-transplant coronary heart disease. Winters et al (1990) in a study of failed human heart allografts reported that body mass index was, of forty risk factors studied, the single most predictive in the development of coronary arteriopathy. However, this data is not consistently supported in the literature. Other researchers have failed to demonstrate obesity as a primary risk factor for the development of CAD, hypertension or hyperlipidaemia, indicating that other factors may play a role (Poindexter et al 1990).

The most frequently demonstrated pattern of weight gain appears to be a steady increase throughout the post-transplant period. Baker et al (1992) demonstrated that changes from baseline weight in transplant recipients were significant at bi-monthly post-transplant intervals, with significant increases between each measure. In another study, ideal body weight increased from 102 per cent at surgery to 113 per cent at one year post-transplant (Poindexter et al 1990). Twenty seven per cent of the patients in this study were classified as obese. Similarly, Grady et al (1990) reported significant weight increases in the post-transplant population which remained elevated over the first three post-operative years. A comparable pattern has been shown in other organ transplant populations (Gardiner 1993).

Corticosteroid administration has been implicated as the major cause of weight gain following transplantation. Heart transplant recipients are prescribed corticosteroids as a means of suppressing immune responses which may initiate rejection of the donor heart (Reynolds 1989). Long term patients are usually sustained on low "maintenance" doses, whilst dosage is increased in periods of acute rejection. The means by which corticosteroids induce changes in body weight can be attributed to both the stimulation of appetite and metabolic effects as a result of increased gluconeogenesis (Elasser and von Eickstedt 1992) . An additional side effect, Cushings Syndrome, whereby the function of the adrenal cortex is suppressed, is related to the development of obesity, facial

rounding and oedema (Garrow 1985). Early studies on the side effects of corticosteroids demonstrated that muscle wasting and increased fat stores were commonly exhibited (Schnieder 1977). Evidence of fat redistribution from peripheral to truncal regions has also been suggested (Melby 1974). Hence the profile of weight changes appear to be gain in total body fat (and resultant weight) as well as notable increases in adipose in the abdominal region as a result of corticosteroid treatment. This pattern appears to be similar to that which poses the greatest cardiovascular risk.

Studies on corticosteroid-free immunosuppressed patients support the earlier evidence for a role of steroid therapy in weight gain. Hagan et al (1990) in a retrospective comparison of steroid versus non-steroid treated heart transplant recipients reported a mean weight difference of 4.2 kilograms between the two groups, with those receiving steroids being of a significantly greater weight. It is notable however, that the researchers did not control for the influence of dietary intake, hence weight changes may not be attributable solely to steroid therapy. Another study by Lake et al (1993) found similar weight increases with steroid administration, however these did not reach statistical significance. Interestingly, it was also demonstrated in both of the above mentioned studies, that those who were obese prior to undergoing transplantation gained significantly more weight in the post-transplant period. Changes in body fat distribution were not examined by these investigators. The findings of the available research to date suggest a probable role for corticosteroid induced weight gain. Further research would be beneficial to discriminate contributing factors.

Despite anecdotal evidence for changes in body composition in heart transplant recipients, supporting evidence from the literature is scarce. One study undertaken by Kavanaugh et al (1989) using skinfold measurements assessed 36 heart transplant patients at a mean time of seven months post-transplant. They described changes in body composition as reductions in fat-free mass, body mass index and percentage body fat. These findings differ from the proposed body composition changes suggested by other researchers.

However only six of the subjects were receiving steroid therapy during the study period, the results therefore are not comparable with corticosteroid immunosuppressed transplant populations. More recently the body composition of transplant recipients maintained on steroid therapy have been assessed using hydrostatic weighing. Keteyian et al (1992) in a study on 24 patients at a mean 21 months post-transplant noted increases in body weight and percentage body fat which reached statistical significance. The mean weight gain for this group of patients was 9.7 kilograms and body composition was reported to be 34 per cent fat, ranking participants on the 15th percentile for body fat when compared to the general population. The prednisone dose and length of post-operative period were inversely related although not additive in their effect on body density. The weight changes indicated in this study are comparable with the 12 kilogram increase at 24 months post-transplant reported by Poindexter et al (1990). However, it is considerably greater than the four kilograms weight gain demonstrated in another study (Keogh et al 1988). These inconsistencies are possibly attributed to the differing periods at which patients were assessed or variations in medication protocols.

In heart transplant recipients, evidence for increased abdominal or android fat distribution remains largely undocumented. In other patients populations treated with steroids, however the proposed increased abdominal distribution of body fat has been questioned. Horber et al (1986) using computed tomography found that patients on long term glucocorticoids exhibited normal or even increased mid thigh fat areas as well as increased central fat stores. This led the researchers to conclude that the traditional concept of fat redistribution from the peripheral to central regions as a result of steroid treatment requires revision. It is still notable however, that both intra-abdominal and subcutaneous central adiposity, did in fact increase and muscle wasting as originally described was evident. Therefore although a typical android pattern may not be manifested in these patients, the metabolic implications of increased abdominal fat stores are still likely to result. Further evidence specifically related to heart transplant recipients is needed to clarify these issues.

Apart from corticosteroids, a number of other factors have been suggested to predispose transplant recipient to obesity. Improvements in quality of life for example, may play a major role in post-transplant weight gain. Patients frequently exhibit enhanced feelings of well being and thus are able to resume an adequate oral diet. In the long term, this may result in excess in caloric intake. In addition improved gastrointestinal absorption of nutrients in post-transplant patients and may impact upon body weight (Keogh 1987). Further, factors such as physical inactivity and fluid retention may contribute to weight changes (Grady and Herold 1988).

In summary, it is evident that overweight and obesity are significant complications of cardiac transplantation. The underlying cause of this appears to be multifactorial. In the long term transplant recipients, maintaining a healthy weight is likely have desirable consequences on lipid profiles, blood pressure, glucose tolerance and cardiac function which may have positive implications for CAD prevention.

2.4 DIABETES MELLITUS

2.4.1. Diabetes and Coronary Heart Disease

Diabetes mellitus is a disorder characterised by a deficiency or reduced sensitivity of insulin with resultant blood glucose elevations and metabolic aberrations. In the long term, both insulin dependant and non-insulin dependant individuals are at increased risk of developing multiple chronic complications including atherosclerosis (McDonald and Roberts 1990). Consequently, coronary heart disease affects a large proportion of individuals with diabetes and is a major cause of morbidity and mortality in this population (Zimmet and King 1986; Moss et al 1991; De Stafano 1993).

The development of atherosclerosis and the resultant cardiovascular complications have been attributed to the interaction of several key factors. Lipid abnormalities including elevations in total cholesterol, LDL cholesterol, HDL cholesterol and triglyceride levels are extensively demonstrated in this population and are thought to result from alterations in lipoprotein metabolism (Briones et al 1984; Reaven 1987). Plasma lipids have been shown to vary depending on glycaemic control, body fat composition and the development of diabetes related complications such as nephropathy (Dunn 1990). Diabetes has been related to hypertension, which may induce endothelial damage thus atherosclerosis. There is also evidence of hyperinsulinaemia playing a role in the atherosclerotic process through its influence on lipid synthesis and deposition (Skinner 1993). Other contributing factors include obesity and blood platelet malfunctioning both of which are prevalent in diabetes mellitus (Felber 1992; MacRury et al 1993).

Large controlled studies have shown that the occurrence of coronary heart disease is increased in diabetes mellitus. The *Framingham Study* demonstrated that the incidence of cardiovascular complications was doubled in diabetic males and tripled in diabetic females when compared to control subjects (Kannel and McGee 1979). More recently,

other investigators have reported that blood glucose concentrations are correlated with cardiovascular risk (Welin et al 1992). Numerous other studies have confirmed such a relationship between diabetes mellitus and coronary heart disease (De Stafano et al 1993; Stamler et al 1984).

2.4.2 Diabetes and Cardiac Transplantation

Diabetes Mellitus has been demonstrated in various studies on post-cardiac transplant recipients (Ladowski et al 1989; Rhenman et al 1988). There are three possible scenarios which may explain the development of diabetes in this setting. Firstly, recipients may exhibit pre-existing insulin or non-insulin dependant diabetes (Rheman et al 1988). Alternatively, post-transplant obesity may initiate the glucose intolerance and hyperinsulinaemia characteristic of diabetes. A final possibility is the use of immunosuppressant medications which may induce metabolic changes and lead to the development diabetes mellitus (Elasser and von Eickstedt 1992). It is also plausible that a combination of these factors results in the post-transplant development of this disorder.

Although diabetes mellitus has been established as a risk factor for the coronary heart disease seen in the general population, evidence for a role in post-transplant CAD has not been widely reported. A study by Ladowski et al (1989) attempted to determine the impact of post-transplant diabetes mellitus on survival following heart transplantation. They reported a three year survival rate of 75 per cent in transplant recipients with diabetes which compares favourably with survival for the non-diabetic transplant population. Similar findings have been reported by other researchers (Rhenman et al 1988). In the same study, Ladowski et al (1989) failed to demonstrate any difference in the development of CAD in patients with diabetes when compared with the total transplant population. Eich et al (1991) additionally failed to find any differences in the incidence of CAD between patients with and without diabetes at six months post-transplant. However, the small sample size and demonstrated low incidence of CAD in the total population at six months post-transplant make the validity of these findings

questionable. Overall, the present lack of research makes it difficult to either support or dispute the role of post-transplant diabetes mellitus in CAD. However, it is still important to recognise that diabetes in the post-transplant period may have adverse consequences for the development of other risk factors, such as hyperlipidaemia (Taylor et al 1989).

Diabetes mellitus has been reported to affect from 8 to 14 per cent of the cardiac transplant population (Utresky et al 1987; Ladowski et al 1989). This is comparable with the prevalence rates demonstrated in other organ transplant populations (Boudreaux et al 1987). However, it is possible in heart transplant patients that glucose intolerance and hyperinsulinaemia occur frequently without the development of diabetes per se. This suggestion is supported by Kemna et al (1994) who reported that male heart transplant recipients had significantly higher plasma glucose and insulin concentrations in response to an oral glucose tolerance test than matched controls. A large proportion of transplant recipients may therefore be at high risk of developing this disorder.

Corticosteroid administration is the most widely reported aetiological factor in the development of diabetes following cardiac transplantation. The term *steroid diabetes* has been used to describe the effects of this immunosuppressant on carbohydrate metabolism and thus blood glucose levels. Corticosteroids have been shown to enhance gluconeogenesis, with resultant increases in blood glucose levels of up to 20 per cent. In addition, both tolerance to glucose and insulin sensitivity generally decrease. Pancreatic function however, is not affected by steroid administration and ketosis does not characteristically develop. The result is a dose dependant steroid induced diabetes mellitus distinguished by a low insulin sensitivity and renal glucose threshold (Elasser and von Eickstedt 1992). Studies in recipients of renal transplants have demonstrated the existence of a relationship between steroid therapy and the development of diabetes mellitus (Friedman et al 1985; Boudreaux et al 1987). In contrast, the few studies on

heart transplant patients to date have failed to find this effect, suggesting that other factors may play a role in this disorder (Ladowski et al 1989).

The immunosuppressant cyclosporine may be additional factor which contributes to the development of post-transplant diabetes mellitus. Animal studies offer support for this hypothesis. Experiments on rats have demonstrated that cyclosporine has the potential to impair glucose tolerance, initiate blood glucose elevations and adversely affect pancreatic islet function (Hahn et al 1986). Thus a cyclosporine induced diabetes mellitus may result. The animal model however, is not strongly supported in studies on human transplant populations. Ladowski et al (1989) failed to find any relationship between cyclosporine dosage and the development of diabetes in heart transplant recipients. Whilst Harris et al (1986) reported similar findings in recipients of renal transplants. Further, Boudreaux et al (1987) indicated that cyclosporine combined with other immunosuppressive medications and recipient characteristics, such as age, contributed to the development of diabetes mellitus following renal transplantation. Again, the scarcity of evidence in the literature, particularly with the heart transplant population, make conclusions regarding cyclosporine and post-transplant diabetes, controversial.

Studies reporting on other factors which may predispose heart transplant recipients to diabetes mellitus are limited. Obesity is one such factor which is known to enhance glucose intolerance, yet its role in post-transplant diabetes mellitus has not been elucidated. One study by Boudreaux et al (1987) on renal transplant recipients reported that the incidence of post-transplant diabetes mellitus was greater in patients weighing over 70 kilograms. Similar evidence in the heart transplant population has not been reported in the literature. Other factors potentially influencing the development of diabetes, such as age and sex have also been largely ignored in the literature to date.

In summary, although post-transplant diabetes mellitus has not been demonstrated to affect CAD risk as such, strong evidence from studies in the non-transplant population

clearly suggest that it is a potential contributing factor. As a result, efforts to reduce the occurrence of this disorder and enhance glycaemic control may be beneficial to the long term cardiovascular profile of transplant recipients. Such attempts would be improved with further research into initiating factors in the development of post-transplant diabetes mellitus.

2.5 HYPERTENSION

2.5.1 Hypertension in Coronary Heart Disease

Hypertension has been well established as a major risk factor for coronary heart disease which affects a large proportion of the Australian population (National Heart Foundation 1989). A diastolic and a systolic blood pressure exceeding 95 and 150 mmHg respectively characterise this disorder which has been shown to increase the risk of coronary heart disease by up to 40 per cent (Stamler et al 1993).

The cardiovascular effects of long term elevations in blood pressure are significant. Hypertension has been shown to accelerate the development of atherosclerosis through its damaging effects on the endothelium (Weber 1994). Uncontrolled blood pressure also increases the workload of the heart and may contribute to cardiac failure (Skinner 1993). In addition, hypertension frequently co-exists with other risk factors including hyperlipidaemia, obesity and diabetes mellitus (Hansson 1992). Thus the risk of heart disease is further increased.

Multiple long term studies have documented hypertension as a cardiovascular risk factor. The *Multiple Risk Factor Intervention Trial* demonstrated that the relationship between blood pressure and coronary heart disease was continuous, graded, strong and independent of other risk factors (Neaton and Wentworth 1992). In the same study, hypertension was estimated to be responsible for 49 per cent of deaths from heart disease. An earlier study reported that the risk of mortality from heart disease was 1.6 times higher in males with a systolic blood pressure above 130 mmHg (Paffenberger et al 1978). A number of more recent published reports also document the significant relationship of blood pressure elevations to coronary heart disease risk (Reed et al 1987; Kannel 1990).

2.5.2 Hypertension following Cardiac Transplantation

In heart transplant recipients, hypertension is the most frequently observed of all conventional cardiovascular risk factors. The role of this disorder in the CAD seen in heart transplant recipients however, is not clear. Some studies have failed to demonstrate any correlation between the presence of this anomaly and the subsequent development of post-transplant CAD. Eich et al (1991) for example, in a study of 38 heart transplant recipients reported that the relationship between hypertension and CAD was insignificant at three years post-transplant. However, the small sample size used in this study may not accurately demonstrate the true implications of uncontrolled hypertension. In contrast, there is some evidence to suggest that hypertension may be a contributing factor to the genesis of post-transplant CAD. Radovancevic et al (1990) confirmed that post-operative arterial hypertension correlated significantly with the onset of CAD. Whilst, Winters et al (1990) reported that a diastolic blood pressure above 90 mmHg when combined with other risk factors had a cumulative influence on arterial lumen narrowing. This effect however, did not occur independently. In addition to these findings, Shapiro et al (1990) have suggested that blood pressure elevations are detrimental to the integrity of the transplanted organ and contribute to considerable morbidity in the post-transplant population. Although the evidence to date is limited, it is possible therefore, that adequate blood pressure control may be of some assistance in the prevention of CAD following cardiac transplantation.

Blood pressure elevations are a frequent occurrence following orthotopic heart transplantation. The exact prevalence is difficult to determine due to the lack of available data, the small sample size and varying definitions of hypertension used in the available studies. However, blood pressure elevations have been demonstrated in up to 90 per cent of cardiac transplant patients (Renuld et al 1989). The time course for the development of this disorder shows variation in the literature. Olivari et al (1989) for example, suggested that, at two weeks following transplantation 68 per cent of patients were hypertensive, whilst at six months the prevalence was 92 per cent. It is important to

recognise however, that the investigators defined hypertension as a blood pressure above 140 / 90 mmHg, a level below the currently accepted definition of hypertension. Ozdogan et al (1990) on the other hand reported that the probability of hypertension (blood pressure > 150 / 95 mmHg) was 52 per cent at one year, 67 per cent at two years and 73 per cent at three years, indicating that this disorder increases progressively with time. In addition, Shapiro et al (1990) demonstrated that the mean initial onset occurred at 50 days post-operative and ranged from one week to six months following transplantation, suggesting that the development of hypertension is highly variable amongst individuals following heart transplantation.

A multitude of factors are thought to impact upon the development of hypertension in transplant recipients. Physiological changes following transplantation are thought to play a role. Denervation, which occurs as a consequence of transplanting the human heart has been shown in some studies to contribute to this problem via the loss of afferent receptors within the heart which influence blood pressure (Shapiro et al 1990). Post-operative volume changes are thought to promote immediate post-transplant hypertension. However, this does not explain the long-term existence of blood pressure elevations. An alternative explanation which has been offered is the increased peripheral resistance noted in heart failure, persisting in the presence of a transplanted heart (Shapiro et al 1990).

In addition to physiological changes, immunosuppressive protocols may also be inductive of hypertension. Cyclosporine is thought to be the major culprit in this process. The mechanism by which this immunosuppressant increases blood pressure is controversial. Regardless of this, there is little dispute that it plays a significant role in hypertension development. The nephrotoxicity of cyclosporine is well documented (Myers et al 1984; Martin et al 1987), thus the effects on renin and angiotensin activity make a likely contribution to hypertension (Shapiro et al 1990). This effect however, has been disputed in the literature, with some researchers reporting the absence of major

abnormalities in the activity of these enzymes with cyclosporine administration (Bellet et al 1985). Furthermore, some studies have failed to find any association between cyclosporine dose and blood pressure, indicating that nephrotoxicity may be unrelated to this condition (Ozdogan et al 1990). An alternative explanation for the effects of cyclosporine come from animal studies which suggest that this immunosuppressant is a direct vasoconstrictor, thus a potential blood pressure elevator (Rego et al 1988). Although the mechanisms by which cyclosporine affects blood pressure remain unclear, it is evident that it plays a significant role in post-transplant hypertension.

The finding that hypertension also occurs in transplant patients not receiving cyclosporine implies that other factors potentially contribute to this disorder (Ozdogan et al 1990). These factors may include recipient characteristics such as a predisposition to hypertension, age, family history of cardiovascular disease or recipient sex (Ozdogan et al 1990). The effects of donor characteristics however, have not been widely reported. Obesity may also influence hypertension development as it does in the general population. Olivari et al (1989) observed that normotensive patients had less post-transplant weight gain than the transplant population as a whole. However, these difference failed to reach statistical significance. In addition, there is some evidence to suggest that corticosteroids play a role in the elevation of blood pressure through the effects on arteriole sensitivity and sodium retention (Shapiro et al 1990). However, few studies to date have investigated these effects.

It is therefore evident that hypertension is a complication of cardiac transplantation which concerns a large proportion of this population. Although the effects of blood pressure elevations on long-term outcomes of heart transplantation have not been defined it is plausible that this disorder has adverse consequences for CAD development. Pharmacological management and careful patient monitoring are likely to assist with blood pressure control. Dietary and lifestyle factors such as weight reduction are

additional modes of therapy with few adverse side effects, thus their role in both the treatment and prevention of this disorder is likely to be beneficial.

2.6. DIETARY INTAKE

2.6.1 Diet in Coronary Heart Disease

Diet has been identified as a corner stone in both the prevention and treatment of cardiovascular diseases. Appropriate dietary modifications have been suggested to reduce the risk of coronary heart disease by up to 20 per cent in the general population (Gotto et al 1990). Decreased body weight, total cholesterol, LDL cholesterol, blood pressure, blood triglycerides as well as increased HDL cholesterol have been shown to be the result of dietary intervention (Schaefer et al 1981; Grundy and Denke 1990; Cheung et al 1994). Although estimates vary as to the effect of diet on reducing cardiovascular risk, it is generally agreed that it is a safe and effective means of heart disease prevention.

Predominant dietary factors in coronary heart disease include fat, cholesterol, sodium and alcohol. Both total fat intake and fatty acid ratios are important in cardiovascular risk reduction. The proportion of total fat in the diet with respect to energy intake is associated with heart disease risk. This relationship, however, is not independent and is thought to be mediated through the effects of fat intake on body weight, and the association of a high fat intake with an increased intake of saturated fatty acids (Shrapnel et al 1992).

The ratio of saturated, polyunsaturated and monounsaturated fatty acids is thought to be more influential. Diets high in saturated fat, through their influence on LDL and total cholesterol, have a significantly negative effect on heart disease risk (Keys et al 1986). This relationship is strong and independent (Kromhout et al 1989). The role of polyunsaturated fats is more controversial. The omega-3 polyunsaturated fatty acids have been shown to reduce post-prandial lipemia, serum triglycerides and the tendency to thrombosis (Mackness et al 1994; Zamperas et al 1994). Whilst omega-6 polyunsaturated fats are thought to have an independent cholesterol lowering effect

(Shrapnel et al 1992). However, detrimental effects of polyunsaturated fat consumption have also been suggested (Hodgson et al 1993). Monounsaturates, once thought to have a neutral effect on serum cholesterol, have been shown to reduce LDL cholesterol when substituted in the diet for saturated fats (National Health and Medical Research Council 1992). More recently, trans fats, resulting from the hydrogenation of vegetable oils, have come into focus as an additional dietary consideration. Evidence however, suggests that the effects of these fats on cholesterol levels are less than saturated fatty acids found in animal products (Zock and Katan 1992). Consequently, dietary modifications of fatty acids plays an important role in heart disease prevention.

The benefits of dietary cholesterol reduction have been met with much controversy. A large number of studies investigating the relationship between cholesterol intake and heart disease risk have produced inconsistent findings. However, it is thought that dietary cholesterol may increase the risk of heart disease in *sensitive* individuals who cannot down-regulate endogenous cholesterol synthesis in response to exogenous intake (Shrapnel et al 1992). Hence modifying dietary cholesterol intake may be advantageous.

The intake of dietary sodium has also been related to the risk of cardiovascular diseases (Elmer et al 1991). A high salt intake, in excess of physiological requirements, is implicated in the development of hypertension. It is thought that this effect may be even stronger in a subset of individuals who are *sensitive* to the effects of sodium (Shrapnel et al 1992). As a total population approach to the prevention of cardiovascular diseases, sodium restriction is controversial (Pecker and Laragh 1991). However, to date, there is little evidence of adverse consequences of dietary sodium reduction (Elmer et al 1991). Some researchers have even suggested that population based sodium restriction to 50 to 100 mmol daily may reduce the population mean blood pressure and reduce requirements for anti-hypertensive pharmacological treatment (Beilin 1992). It is likely therefore, that sodium restriction is a valid dietary action, particularly in high risk individuals.

Alcohol intake, depending on the level of consumption, can be detrimental or possibly beneficial to heart disease risk. Excessive alcohol consumption has been observed to increase serum triglycerides and blood pressure thus heart disease risk (Ahlawat and Siwach 1994; Stamler et al 1991). In addition, heavy drinkers may be at increased risk of other cardiovascular consequences including sudden cardiac death and cerebrovascular accidents (Lester 1994). On the other hand, small quantities of alcohol, consumed on a regular basis may offer a protective cardiovascular effect via its influence on HDL cholesterol and platelet reactivity (Renaud and de Lorgeril 1992; Ganziano et al 1993). Although it remains controversial as to whether the high density lipoprotein cholesterol sub-class elevated by alcohol actually confers any cardiovascular benefits (Diehl et al 1988). As a result, reduced alcohol consumption is recommended.

An increased intake of carbohydrates and dietary fibre is recommended as an adjunct to healthy heart diet therapy. The benefits of such a dietary pattern include reduction in fat intake because of dietary substitution with these nutrients. Whilst fibre, particularly the soluble variety has been shown to reduce total and LDL cholesterol through faecal bile losses (Anderson et al 1991). Thus the benefits of increasing both fibre and carbohydrate intake are evident in both heart disease prevention and treatment.

Diet clearly plays a role, both in the establishment and prevention of coronary heart disease in the general population. Current dietary recommendations advocate a total fat intake of less than 30 per cent of energy, with saturated fat accounting for less than 10 per cent of total energy intake. Sodium intake is recommended to be less than 100 mmol per day and cholesterol below 300 milligrams per day, whilst alcohol intake should not exceed 20 grams daily for women and 40 grams each day for men. In addition, fibre intake is encouraged (Stewart 1990; Thomas 1994). Ideally, dietary intervention should achieve a body weight appropriate to height (as indicated by BMI), blood cholesterol levels below 5.5 mmol/L, triglycerides less than 1.8 mmol/L, and diastolic and systolic

blood pressure less than 90 and 150 mmHg respectively (Curtin University of Technology 1992; Dwyer 1995).

2.6.2 Diet in Cardiac Transplantation

In heart transplant recipients, the role of diet in the aetiology of post-transplant CAD is not as clear. The influence of pharmacological, immunological and infectious factors in conjunction with a lack of available research, makes it difficult to ascertain the extent to which diet can be implicated in the establishment of, or assist in the prevention of cardiovascular complications.

Nutrition care of the heart transplant patient generally occurs as a three step process. Prior to transplantation, patients often require intervention as a result of muscle wasting, hypermetabolism and protein and fat malabsorption (Kumar and Coulston 1983). Immediately post-transplant, patients may exhibit anorexia and post-operative catabolism that warrants supplemental or enteral nutrition (Frazier et al 1985). However, more frequently, appetite and nutritional status are significantly improved (C. Rawcliffe; Personal Communications 1995). In the long term, the increased risk of developing cardiovascular complications is an indication for nutrition intervention (Poindexter 1992). Pre and immediate post-operative dietary requirements, considerations and interventions are beyond the scope of this study. This review is concerned specifically with the long term dietary management of heart transplant recipients.

At St. Vincent's Hospital, long term nutritional management involves assessment and education by a Clinical Nutritionist. Dietary recommendations are based on a *healthy heart* diet. This includes, less than 30 per cent of energy from fat, less than 10 per cent of energy from saturated fat, less than 300 milligrams of cholesterol per day, an increased dietary fibre intake and no added salt. These dietary guidelines are compatible with those recommended by the *National Heart Foundation* for the prevention of cardiovascular disease in the general population (Shrapnel et al 1992).

Similar guidelines exist in other heart transplant centres. Approximately 80 per cent of transplant centres in the United States include a dietitian as a member of the cardiac support team. The most common long term post-transplant dietary recommendation is a 2-4 gram sodium restriction, low fat, low cholesterol diet. This is advocated in 30 per cent of transplant centres. However, often, a more stringent diet which includes restricted dietary fat to less than 30 per cent of energy, restriction of saturated fat to less than 7 per cent of energy and dietary cholesterol intake of less than 200 milligrams per day is recommended (Moore et al 1991).

The few studies reporting on the diet of post-transplant patients suggest that the dietary intake of this population generally complies with recommendations. Total fat intake has been reported to be approximately 33 per cent of energy in one French study (Salen et al 1994). This is similar to the reported intakes of the Australian population (Baghurst et al 1994). In the same study, saturated, polyunsaturated and monounsaturated fat accounted for 12, 7 and 11 per cent of energy respectively. Alcohol and fibre intakes in this population were reported to be low. The researchers concluded that compliance with the dietary advice provided by doctors or dietitians was high in the post-transplant population (Salen et al 1994). The results of this study, however must be interpreted with care as the twenty-four hour recall as used to assess dietary intake does not account for intra-individual variation in dietary intake (Cameron and van Staveren 1988). Whilst cultural factors reduce the comparability of these findings with the Australian population.

In comparison, subjective assessments of dietary intake as undertaken in some studies indicate that compliance with dietary recommendations is generally sub-optimal. Keogh (1987), in studies on hyperlipidaemia, suggested that compliance with low fat, low cholesterol dietary advice was often poor. This claim was based upon the high incidence of obesity and hyperlipidaemia in this population and was not substantiated with evidence regarding actual dietary intakes. Keogh also noted in her study, the possible role of

lifestyle factors in reducing cardiovascular risk and the need for more stringent efforts for weight control, hence dietary intervention, in the transplant population.

The degree to which current recommendations for the long term management of heart transplant recipients reduce cardiovascular risk, is not known. In renal transplant patients, who tend to have similar clinical profiles, evidence suggests that diet therapy is a safe and effective means of treatment. Dietary modifications including a reduction in saturated fat, cholesterol, simple sugars and alcohol intake have been associated with significant reductions in plasma cholesterol and body weight in this population (Disler et al 1981). Little has been reported on the relationship between these known risk factors and dietary intakes in the heart transplant population.

Ragsdale (1987) has attempted to show improved nutritional status as a result of dietary intervention by comparing nutrition intervention in the initial stages of a post-transplant nutrition program, with later more stringent interventions. The first 10 heart transplant recipients at the Indiana Methodist Hospital were placed on a type IIA hyperlipoproteinemia (less than 300 milligrams of cholesterol), restricted simple sugar, and 2 - 4 gram sodium-restricted diet. Dietary follow up in these patients was limited. Of these patients, five gained 20 kilograms or more above their pre-transplant weight and four died as a result of accelerated CAD within eighteen months. Since the initiation of a nutrition education program which emphasised less than 25 per cent of energy from fat, 10 per cent monounsaturated fat and 10 per cent saturated fats, as well as regular dietetic intervention, a larger proportion of patients were living beyond one year. At the same time, the incidence of obesity and mortality from CAD was reduced. These improvements were attributed to changes in medications, improved dietary monitoring and increased patient and family involvement with dietary modifications. Although this study suggests that dietary intervention may play a role in improving the long term cardiovascular health of transplant recipients, the statistical significance of any changes

and the extent to which improved health outcomes were related to dietary intervention were not reported.

There is some evidence that a Mediterranean style of eating may be effective in the long term management of heart transplant patients. The Mediterranean diet, as popularised by *The Seven Countries Study* is low in total fat, and saturated fat and high in mono-unsaturates, and is associated with a low cardiac mortality rate in the general population (Kromhout et al 1989). In heart transplant recipients, the possible benefits of consuming such a diet include a reduction in LDL cholesterol as a result of a low saturated fat intake, reduced body weight occurring in conjunction with less calories from fat, and a reduced oxidation of lipoproteins to foam cells as a result of the effects of oleic acid, a mono-unsaturate (National Health and Medical Research Council 1992; Kromhout et al 1989). Salen et al (1994) in a dietary intervention study evaluated the effects of the Mediterranean diet on cholesterol levels in post-transplant recipients. Forty one transplant recipients with hypercholesterolaemia were studied for an eighteen month period. They were provided with diet counselling to reduce total fat, saturated fat and polyunsaturated fat to less than 30, 10 and 6 per cent of total energy respectively. Saturated and polyunsaturated fats in the diet were replaced with monounsaturates including olive and rapeseed oils. Participants were advised to avoid rich sources of polyunsaturates, to select low fat dairy products, lean meats and increase fruit, vegetable and cereal consumption, as well as drink moderate amounts of wine during meals.

The mean dietary intake one year after initial counselling was significantly lower in total calories and saturated fat. Intakes of polyunsaturates, cholesterol and total fat were lower, whilst monounsaturated fat intake was higher, these differences however, were not statistically significant. The biochemical profile of participants showed significantly reduced total and low-density lipoprotein cholesterol after diet modification. Body weight did not significantly differ, nor did high density lipoprotein cholesterol levels or arterial blood pressure. Although immunosuppressive therapy was progressively

reduced during the period of the study, there were no significant changes in blood pressure or blood triglycerides. Hence, it was concluded that changes in the biochemical profile of participants was the result of dietary intervention. The potential role of diet as an alternative to pharmacological treatment in these patients is therefore promising. However, the impact of dietary intervention on long term survival could not be determined due to the short time period of the study and absence of a control group. The need for a large controlled study to confirm these findings is warranted.

The benefits of dietary sodium restriction in the post-transplant period have also been implied. Sodium intake has been linked with hypertension in epidemiological studies, clinical trials and animal studies (Shrapnel et al 1992). Singer et al (1994) found similar results in the heart transplant population. In a study on twelve transplant recipients, it was reported that a sodium intake of ten mmol per day substantially reduced systolic blood pressure, whilst a 350 mmol per day intake was associated with increased blood pressure (Singer et al 1994). The effect was similar to that found in non-transplant recipients with essential hypertension. The potential for sodium restriction as a non-pharmacological alternative to the treatment of post-transplant hypertension is therefore evident. However, it must be noted that, in real life, the 10 mmol daily intake of sodium on the low salt diet as implemented in the above mentioned study is largely unachievable and less than recognised human physiological requirements (National Health and Medical Research Council 1991). Further studies are required determine the role of currently recommended level of sodium intake in blood pressure control in this population.

The possible role of a multitude of factors in post-transplant CAD, makes the contribution of diet in both its development and treatment largely controversial. Other studies supporting those of Salen et al (1994) and Singer et al (1994) are limited. There is however, some contradictory evidence which suggests that dietary intervention has little effect on reducing body weight, serum lipids or blood pressure in the post-transplant recipient (Eich et al 1990). Ballantyne et al (1992) in a six year follow up of transplant

patients, reported that the *American Heart Foundation Step One Diet* had little effect on reducing serum cholesterol, triglycerides or LDL cholesterol levels. However, it should be noted that compliance with the dietary recommendations was not measured in this study. Hence, these results may not reflect the true advantages of dietary intervention.

The role of dietary intervention has also been questioned by Becker et al (1988). They found no correlation between LDL cholesterol, total cholesterol or triglyceride levels and dietary fat intake. As a result it was concluded that low levels of dietary fat and cholesterol demonstrate little effect on serum lipids. Again caution must be taken in the interpretation of these results. Firstly, the actual dietary fat intake of the sample was not reported in the study. The results therefore rely on the researchers assessment of what constitutes a low fat diet. In addition, a similar dietary fat questionnaire as that used to measure intake has recently been reported to lack the sensitivity and specificity to be used as a single assessment method (Caan et al 1995). Conclusions regarding dietary intake and contribution to CAD, therefore remain controversial.

Cardiac transplant patients are clearly at high risk of developing long term cardiovascular complications. Although diet has been established as a key factor in the coronary heart disease seen in the general population, risk factors in heart transplant recipients are not as clearly defined. Further investigation into the effectiveness of diet therapy, the dietary intake of this population and the optimum dietary recommendations is needed to assist in the prevention and non-pharmacological management of post transplant CAD.

2.7 MULTIPLE CARDIOVASCULAR RISK FACTORS AND CAD DEVELOPMENT

The evidence from the literature to date clearly suggests that the role of conventional cardiovascular risk factors in the development of CAD following heart transplantation remains highly controversial. Although the underlying cause of CAD in the cardiac transplant recipient has yet to be determined, evidence suggests that a combination of immunological and non-immunological factors influence CAD development. In support of this hypothesis, there is considerable evidence that risk factors including hyperlipidaemia, obesity, hypertension and diabetes mellitus, in conjunction with dietary and lifestyle factors contribute to this anomaly.

Although each of the risk factors have been discussed separately in this report, the multifactorial nature of this disorder is noteworthy. Obesity for example is likely to affect other risk factors such as diabetes and hypertension. Whilst dietary intake has multiple consequences for cardiovascular profile. It has been suggested in some studies that the affect of these risk factors is additive on CAD development. Winters et al (1990) demonstrated that percentage luminal narrowing was increased with the successive addition of each conventional cardiovascular risk factor in cardiac transplant recipients. In patients with a BMI >27, they reported a rise in luminal narrowing from 66 to 80 per cent. This is similar to findings in the general population which have suggested that the existence of multiple risk factors has adverse consequences for cardiovascular profile.

Clearly, an effective means of prevention would be beneficial to both quality of life and survival in this population. However, inconsistencies in the literature to date, warrants further research to investigate the underlying aetiology, prevalence and preventative options for this major limiting factor in the long term survival of cardiac transplant recipients.

2.8. METHODOLOGY

2.8.1 Body Weight Assessment

Body weight can be measured using a number of different anthropometric assessment methods. In the present study, body mass index, waist-to-hip ratio and waist circumference have been selected as determinants of cardiovascular risk.

In clinical practice, the body mass index (BMI) is the most frequently defined measure of overweight and obesity. BMI is a measure of the ratio of weight (kg) to height (m)2 and is useful for comparing body weights between persons of differing height. A BMI in excess of 25 is constitutes overweight, whilst that greater than 30 is characteristic of obesity (Bray 1985). These classifications are shown in table (1) below.

BMI	CLASSIFICATION
<19	Underweight
20 - 25	Healthy Weight
26 - 30	Overweight
31 - 40	Obese
>40	Morbidly Obese

Table 2.7.1 Classifications of Body Weight based on BMI

(Adapted from Bray 1985)

The BMI is advantageous as a measure of body weight in that it is easy to calculate and provides a simple total body weight classification criteria which can be used to assess potential health risks (Bray 1985). However, this technique of anthropometric assessment provides little information on the distribution of body fat and there is some evidence that BMI is not predictive of cardiovascular risk (Loos and Halais 1991; Hodgson et al 1994). Some researchers have also suggested that the BMI misclassifies

obese patients when compared with measures of body fat (Hortobagyi et al 1994). Thus methods to assess body composition may provide a more useful indication of cardiovascular risk than total body weight.

One of the most commonly employed methods to determine the site of fat deposits is the waist-to-hip ratio (WHR). The WHR assessment technique involves measuring both the waist and hips with a non-stretchable tape measure and calculating the resultant ratio. The validity of this method for determining body fat distribution has been reported by Loos and Halais (1991) who established that this measure was a valid means of identifying increased cardiovascular risk and increasing abdominal fat deposition. Ross et al (1992) on the other hand, compared similar anthropometric variables with magnetic resonance imaging and concluded that WHR was not a good indicator of visceral adiposity.

The inconsistencies in the literature on WHR clearly make it difficult to assess the validity of this method for body fat assessment. It is likely that the wide variation in WHR methodologies contributes to methodological problems. To date, over 18 different sites for measuring the waist and hips have been identified (Loos and Halais 1991) each which been reported to significantly alter the WHR (Alexander and Dugdale 1992). Houmard et al (1991) have attempted to clarify this issue by comparing five different sites for WHR assessment with metabolic variables. The results of which suggest that measures at minimal waist / maximal hips, umbilicus / maximal hips, umbilicus / greater trochanters and umbilicus / iliac spine are most strongly associated with indices of lipid and carbohydrate metabolism. Thus it is possible that a number of sites may be utilised to determine the degree of cardiovascular risk.

A potential problem in WHR assessment is the use of different cut-off points to indicate cardiovascular risk. Some researchers suggest that a WHR of <0.9 for males and <0.8 for females are the most desirable for cardiovascular health (Egger 1992). Elsewhere

however, levels of 0.95 and up to 1.0 have been suggested for males and 0.85 and 0.75 for females (Loos and Halais 1991; Despres et al 1992). Clearly, the use of these cut off points is likely to be dependant on the chosen site and will ultimately affect the degree of cardiovascular risk. The cut-off points of 0.9 for males and 0.8 for females have been shown by several researchers to correspond with cardiovascular risk at the site of the umbilicus / iliac spine (Alexander and Dugdale 1992; Egger 1992).

The reliability of WHR assessment technique appears to be satisfactory. Several recent studies have shown that repeated measures produce similar results. Rasmussen et al (1993), demonstrated that intra-observer variation was low in the measurement of WHR and concluded that repeated measurements were not necessary in clinical trials. Other researchers have demonstrated that multiple measures differ by up to 0.62 cm for the waist and 1.24 cm for the hips. As a result, WHR variation is 0.02 (Alexander and Dugdale 1992). Similarly, Loos and Halais (1991) reported the mean difference between two measures of WHR to be less than 1 per cent.

More recently, waist circumference has been identified as a better indicator of abdominal fat distribution and consequent cardiovascular risk. Pouliot et al (1994) compared visceral adipose tissue using computer tomography with measures of waist circumference, abdominal sagittal diameter and WHR. They found that waist circumference measures >100 cm and sagittal diameter >25 cm were the most likely to be associated with the metabolic disturbances which affect cardiovascular risk. This is supported by more recent studies from Lean et al (1995) who demonstrated that waist circumference was useful in identifying increased cardiovascular risk, independent of WHR. Waist circumference could therefore be utilised as either an independant or additional measure of body fat distribution.

2.8.2 Dietary Intake Methodology

The diet history, as described by Burke (1947) is a method of measuring the usual dietary intake of individuals. This process involves an extensive interview to obtain information regarding foods consumed and frequency of consumption and methods of preparation. As with other means of dietary assessment, there are both advantages and limitations to using this method as a tool in research.

The diet history is advantageous in that it requires little time commitment from respondents, as a result, participation rates may be increased (Cameron and van Staveren 1988). As the focus of this method is on *usual* it also allows for the assessment of intake over a longer period than other methods (eg. 24 hour recall, 3 day food records). In addition, it allows for exploration of food preparation techniques and probing for further details regarding intake (Thompson and Byers 1994).

Major limitations of the diet history include the large subjective component required in estimating intake, as participants are required to make judgements regarding usual foods and serve sizes. Thus actual intake is subject to possible misinterpretation. The diet history is also problematic in the fact that data collection requires participants to have a usual dietary pattern. As a result, individuals with inconsistent intakes cannot be included in analysis. In addition, the *usual* aspect of this method, frequently results in omission of less frequent, but possibly important dietary contributions (Freudanheim 1993).

The validity of the diet history method is subject to some controversy. A number of researchers have found that nutrient intakes tend to be over estimated when compared with other methods (Nes et al 1991). Whilst Black et al (1993), have reported that weight-conscious individuals may actually underestimate usual intake with this method. On the other hand, some have suggested that an in depth history is a relatively valid means of dietary assessment (Freudanheim 1993). Whilst, other researchers have

reported a correlation between this method and biochemical indicators (van Staveren et al 1985). However, this has not been consistently demonstrated.

Overall, the diet history method, as with other means of dietary intake assessment is subject to inaccuracies. As a result, it is recommended that nutrient intakes be interpreted as relative rather than absolute. To accommodate this in research, Bourke (1947) has recommendaed that individuals be ranked into high, moderate and low classifications for the range of nutrients examined. As a result, using a range of intakes should reduce inaccuracies evident with this measurement technique.

3. METHODS

3.1 Setting

This project was undertaken at St. Vincent's Hospital (SVH), Sydney from August to November 1995. At the time of writing, SVH was a 400 bed teaching hospital and the only institution performing cardiac transplantation within New South Wales.

3.2 Sample

The sample was selected from the St. Vincent's Hospital heart transplant population who had received a successful orthotopic transplant within the past 12 to 24 months. This time frame was selected because there is evidence to suggest that risk factors for heart disease occur within the first year post-transplant. In addition, biochemical and anthropometric indicators are regularly monitored during this period and are therefore available for analysis.

Fifty four orthotopic heart transplants were performed at SVH from July 1993 to November 1994. Of these, eight patients had died, leaving of 46 transplant recipients. The small size of the transplant population required all patients who met the inclusion criteria to be contacted for participation.

3.3 Inclusion Criteria

For inclusion in the study, the patients had to meet the following criteria:

i) Successful orthotopic heart transplant within past 12 to 24 months

ii) Over 18 years of age

iii) No other medical condition that may affect nutritional status (eg. liver or renal disease, cancer)

iv) No special physiological requirements (eg. pregnancy)

3.4 Participant Contact

Patients who met the above criteria were selected from SVH records. Each person was sent a letter explaining the aims and objectives of the project and the nature and extent of participant involvement (refer to appendix 11.2). This was followed up with a telephone call to each patient. A convenient date (between August and October 1995) and venue was arranged with those who agreed to participate.

3.5 Ethical Issues

Approval was obtained from the SVH and University of Wollongong Ethics Committee's (refer to appendix 11.1). Informed consent was obtained by a written consent form, a copy of which was retained by both the researcher and participant (Refer to appendix 11.3). Each participant was identified by their hospital transplant number to ensuring confidentiality. Information which identified participants was not removed from SVH.

3.6 Data Collection

The study involved two type of data collection - retrospective information from SVH medical records and information provided by the participant. These are described below.

Demographic Data

Data describing the characteristics of each participant, including age, sex, initial diagnosis, medication protocols and waiting period for transplantation was obtained from SVH medical records.

Anthropometric Data

Recent / current body weight was obtained from SVH outpatient medical notes and transplant records. If weight was not recently recorded this was obtained by weighing participants. Pre-transplant body weight, weight at 1, 3, 6, 12, 18 and 24 months post-transplant (as appropriate) was obtained from SVH pre-transplant assessment clinic and

outpatient medical notes. Participants were weighed on the same set of scales at each time interval. However, a number of participants were weighed on a smaller set of scales if their recent weight had not been recorded. The same set of scales was used for each of these participants. Weight was recorded to the nearest 0.5 kg. Height was obtained from SVH pre-transplant assessment clinic records. The accuracy of this information was verbally confirmed with participants. Height was recorded to the nearest 1.0 cm. Waist to hip ratios were determined by measuring participants waist and hips with a plastic tape measure. Waist measurement was determined at the level of the umbilicus, whilst hips were measured at the superior iliac crest. All measurements were taken while participants were lightly clothed and upright with arms at their sides. Each site was measured twice and the average of the two readings was recorded.

Dietary Intake

To obtain information regarding usual dietary intake, participants were each interviewed for approximately one hour. A modified version of Burkes original diet history was the selected method (Burke 1947). The aim of the diet history was to quantify usual dietary intake and derive qualitative information about eating behaviours. Participants were asked to describe their usual dietary intake in as much detail as possible. A food frequency questionnaire was used as a crosscheck and to further quantify diet history data. The three day food record as used by Burke was not included due to time constraints. Food models, standard measures and participant drawings were used to quantify serve sizes.

Participants were also asked a series of additional questions. This included describing methods of food preparation, use of convenience and takeaway foods, and brands and varieties of food products consumed. Each participant was also asked to rate present appetite (poor, good, excellent), changes in appetite since transplantation (increased, decreased, no change) and noticeable changes in weight since transplantation (increased, decreased, no change). Finally, to determine current level of physical activity,

participants were asked if they engaged in any regular exercise and if yes, the duration and frequency of activity.

Biochemical Indicators

Total cholesterol and blood triglyceride levels were obtained from SVH outpatient medical notes and transplant records. These measurements were obtained using standard hospital collection and analysis procedures. This data was recorded at pre-transplant, and 1, 3, 6, and 12 as well as 18 and 24 months post-transplant (where applicable).

Blood Pressure

Blood pressure measurements were obtained from SVH outpatient medical notes and transplant records. This data was recorded at pre-transplant, and 1, 3, 6, and 12 as well as 18 and 24 months post-transplant (where applicable). The administration of anti-hypertensive medications or a diastolic blood pressure exceeding 95 mmHg were considered to constitute hypertension. The degree of blood pressure control over time was noted for this population.

Diabetes Mellitus

The presence or absence of diabetes mellitus was also noted, as was mode of control (eg. diet, oral hypoglycaemic agents, insulin)

3.7 Data Analysis

The collected data was analysed as follows:

Demographic Data

The participants age, sex, medications and initial diagnosis were used to describe the characteristics of the sample. Descriptive statistics were used to provide this information.

Cholesterol Levels

Cholesterol levels were analysed at pre-transplant and 1,3,6,12,18 and 24 months post-transplant using an analysis of variance (ANOVA). A t-test was used to determine any significant changes between each increment. The proportion of patients with hypercholesterolaemia at each point in time was also noted.

Triglyceride Levels

Changes in triglyceride levels were described where available. Due to missing data, these were not statistically analysed.

Body Weight

Weights and heights were converted into the Body Mass Index (BMI). The BMI of participants was analysed at pre-transplant and 1,3,6,12,18 and 24 months post-transplant using an analysis of variance (ANOVA). A t-test was used to determine any statistically significant changes at each increment. Average weight gain at each period and the proportion of patients in the underweight, healthy weight, overweight and obese categories of the healthy weight range were described for the group.

Waist-to-Hip Ratio

The Waist-to-Hip ratio was used to identify the occurrence of abdominal obesity in the post-transplant population. The mean ratios were compared to the recommended values of 0.80 for females and 0.90 for males. A t-test was used to determine any statistically significant differences.

Blood Pressure

Diastolic and systolic blood pressures were recorded at 1,3,6,12,18 and 24 (where applicable) months post-transplant and analysed using an analysis of variance (ANOVA). The proportion of patients with hypertension and degree of blood pressure control was noted over time.

Diabetes Mellitus

The occurrence of diabetes and mode of control were described for this population.

Dietary Intake

Dietary intake data was analysed quantitatively for total fat, saturated, monounsaturated and polyunsaturated fat, carbohydrate, protein, fibre, alcohol, cholesterol and sodium using the Diet Version 2.05 (Xyris Software, Aust. Pty. Ltd. 1989) nutrient analysis program. Dietary intake data was compared to the current nutritional recommendations for heart transplant recipients. A t-test was used to determine the extent to which the mean intake for this population differs from these recommendations. Transplant recipients were ranked into categories according to low, medium or high levels of dietary intake for the analysed nutrients.

4. RESULTS

4.1 Patient Characteristics

Of the 46 patients contacted, 17 were excluded from the study. Two of the patients had developed chronic renal failure, one had liver disease, one was less than 18 years of age, five lived interstate and were not attending SVH during the period of the study and eight were not able to be contacted. Of the remaining 29 patients, two declined to participate. The remaining 27 patients made up the study population.

Table (1) lists the demographic characteristics of the patient population including age, sex, time since transplantation and pre-transplant waiting period.

Variable	*Mean ±SD*	*Range*
Age (years)	48.7 ± 7.9	(36 - 66)
Sex	Male: 23	
	Female: 4	
Post-transplant Period (months)	17.7 ± 4.67	(11 - 25)
Waiting Period (days)	137 ± 162.8	(1 - 546)

Table 4.1: Characteristics of the patient population (N= 27)

Age was recorded as that at time of participation in the study. The age range of participants was from 36 to 66 years, with mean of 48.7 years. Time since transplantation was also recorded at time of participation. The post-transplant period ranged from 11 to 25 months with a mean of 17.7 months. This deviation from selection criteria is the result of participant availability. There were more males than females

participating in the study, with a male to female ratio of approximately 6:1. This is similar to the pattern seen in the total transplant population. Mean waiting period for transplantation was 137 days. Waiting time ranged from one to 546 days, depending on the availability of a of suitable donor.

The pre-operative diagnoses for the study population are shown in Table 4.2. The most frequent diagnosis requiring transplantation was idiopathic cardiomyopathy or disease of the myocardium of unknown cause. Second to that was ischaemic heart disease, followed by valvular myopathy. Less frequent diagnoses included myocarditis, congenital heart disease and peripartum myopathy.

Diagnosis	*Number*
Idiopathic Cardiomyopathy	13
Ischaemic Heart Disease	9
Valvular Myopathy	2
Myocarditis	1
Peripartum Myopathy	1
Congenital Heart Disease	1

Table 4.2: Pre-operative diagnosis of heart transplant recipients (N=27)

All participants in this study were receiving triple-drug immunosuppression with prednisone, azathioprine and cyclosporine. Two participants were also receiving Adifax, an appetite suppressant, at the time of the study.

4.2 Lipid Levels

Hyperlipidaemia was defined as a serum cholesterol exceeding 5.5 mmol/litre, triglyceride levels greater than 1.8 mmol/litre or by the administration of lipid lowering agents. Prior to transplantation, 30 per cent of patients displayed hyperlipidaemia. At three months this increased to 44 per cent and at twelve months 41 per cent of transplant recipients were hyperlipidaemic. Figure 4.1 shows these results.

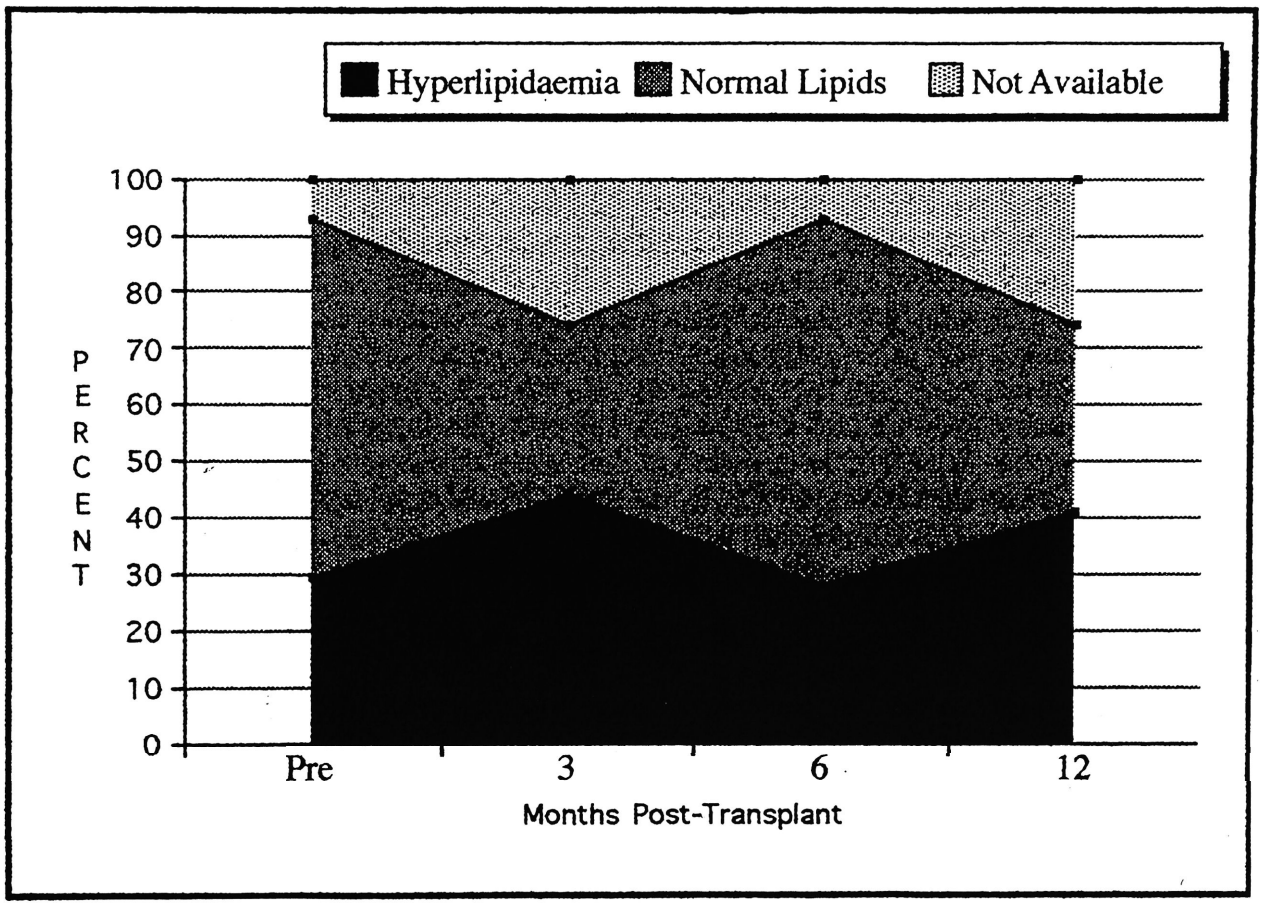


Figure 4.1: The frequency of lipid elevations following cardiac transplantation

Mean total cholesterol levels were found to differ over time with an analysis of variance (ANOVA). A t-test was performed to test the significance of any differences at each interval in time. Prior to transplantation the mean cholesterol level was 4.4 ± 1.3 mmol/litre. At three months post-transplant, this increased significantly ($t=-2.86$ $p<0.01$) to 6.1 ± 1.6 mmol/litre. Over time, cholesterol remained elevated at a mean of 5.8 ± 1.1 mmol/litre, 5.5 ± 0.8 mmol/litre and 5.5 ± 0.95 mmol/litre at six, twelve and eighteen months respectively. However, no further significant increases in cholesterol occurred after this time. In addition, the mean cholesterol for the four patients at 24 months post-transplant was 5.3 mmol/litre. Figure 4.2 represents these results.

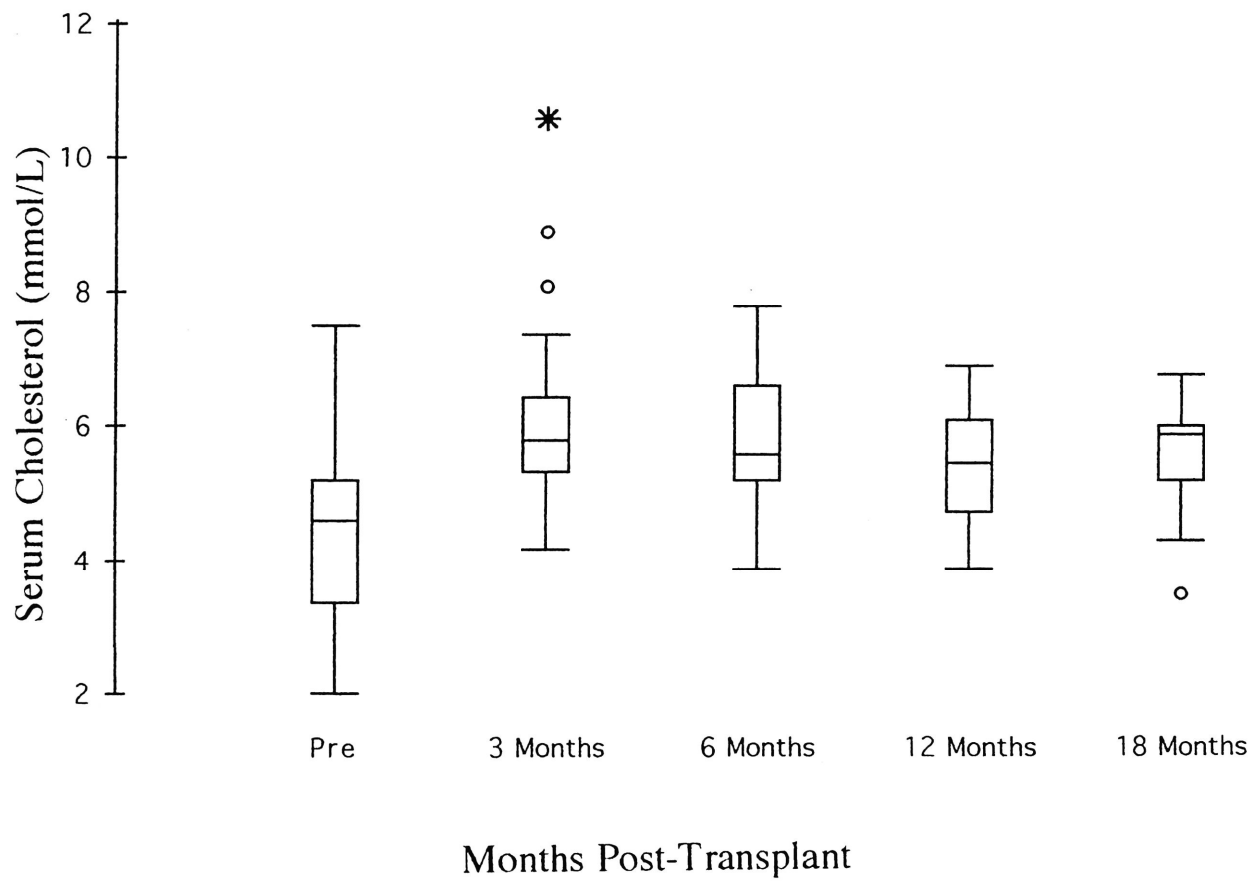


Figure 4.2 : Changes in total cholesterol over time in cardiac transplant recipients

Triglyceride levels over time, were not readily available for all patients. Statistical analysis of these results was therefore not performed. Figure 4.3 below shows a trend to increasing triglycerides at 3 months post-transplant, with a progressive decline over the following months.

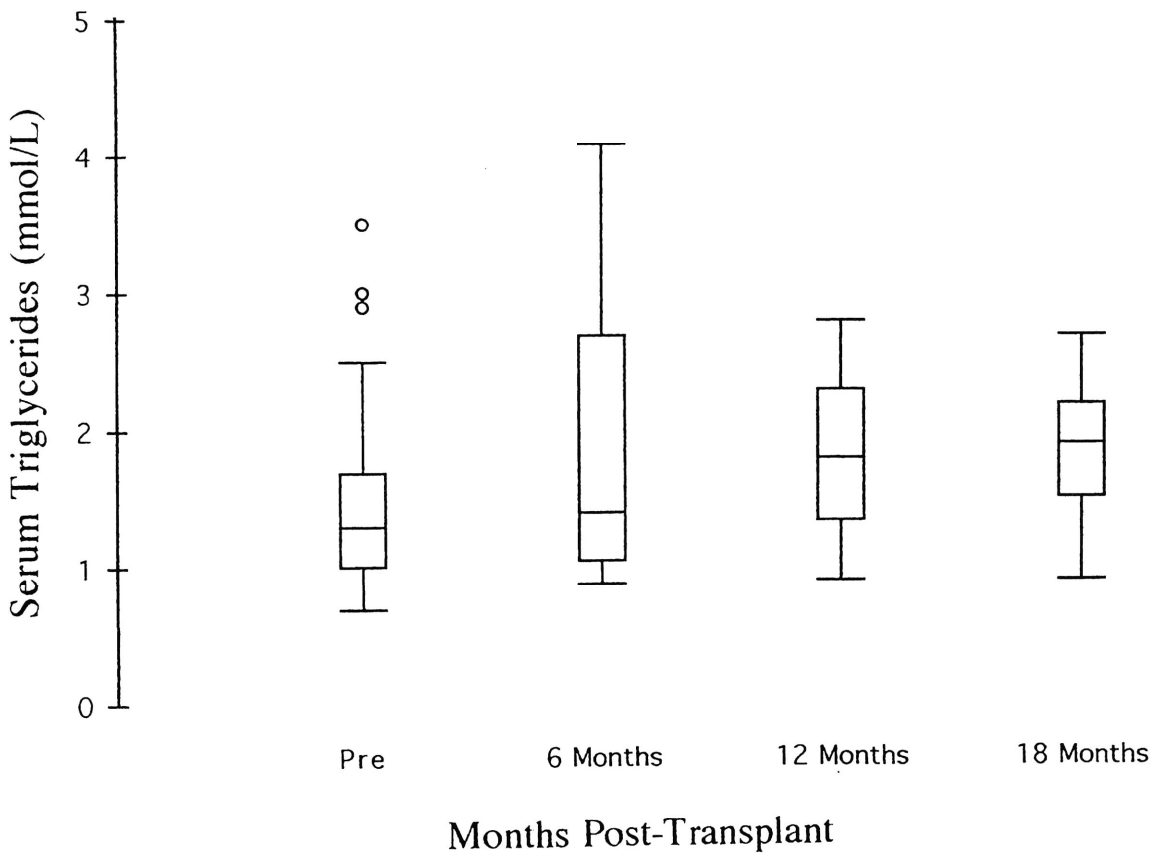


Figure 4.3: Changes in triglyceride levels over time in cardiac transplant recipients

4.3 Body Weight

Participants were classified as being underweight, healthy weight, overweight or obese as calculated by BMI. The proportion of heart transplant patients in the overweight and obese categories of the healthy weight range increased with time from one month post-transplant. Prior to transplant, 44 per cent of patients were above the desirable weight for height, at one month post-operative, this decreased to 22 per cent of patients. After this time the number of overweight and obese patients increased to 52 per cent at three months, 56 per cent at six months and by twelve months post-transplant, 56 per cent of recipients were overweight, with one third of these being classified as obese. The number of patients in the underweight and healthy weight ranges showed a corresponding decrease with time. Refer to Figure 4.4.

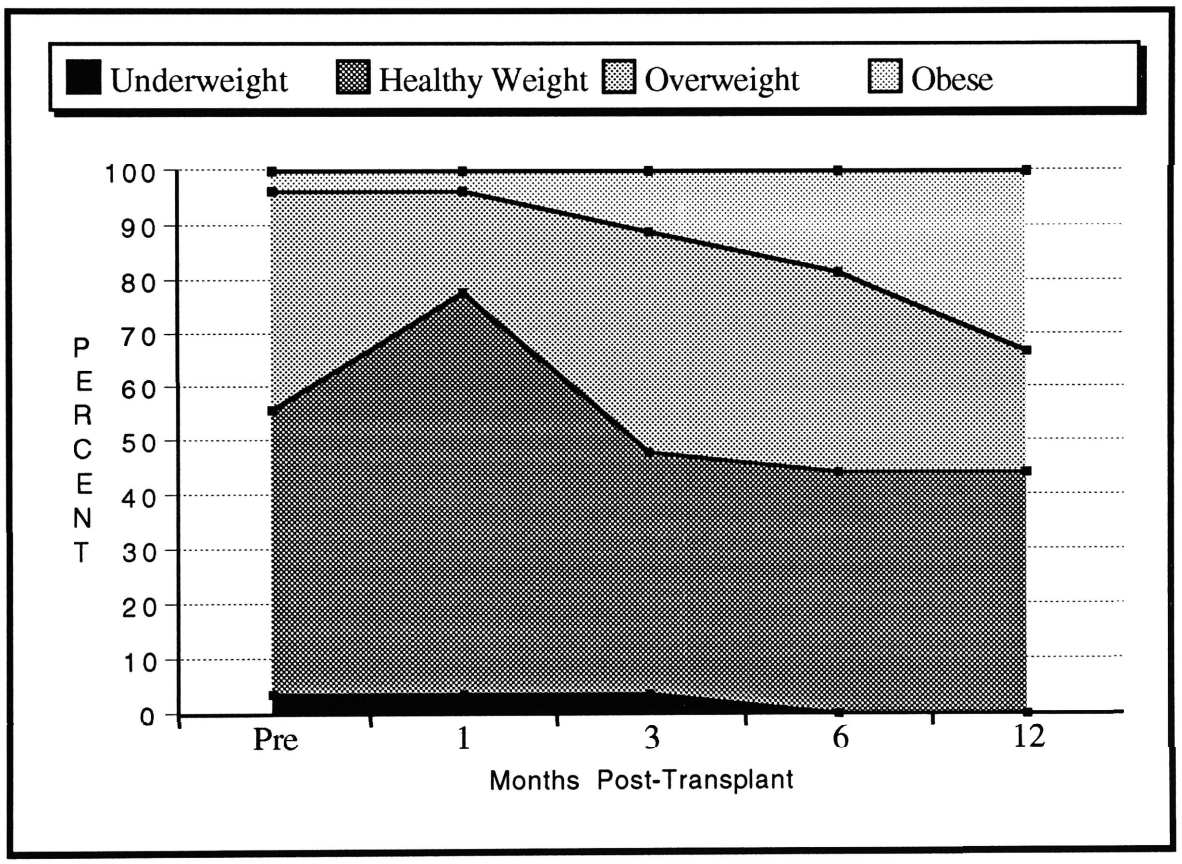


Figure 4.4: Weight status of the post-cardiac transplant population over time

Changes in body weight were evident over time with an analysis of variance (ANOVA). A t-test was performed to determine the significance of these changes. The mean body mass index for participants prior to transplantation was 24.7 ± 3.3. At one month post-operative this decreased significantly to 23.9 ± 3.5 ($t=3.18$ $p<0.01$). A steady increase in body weight that was significant at each increment was evident from three months post-transplant, up to twelve months. At three months mean weight increased to 25.1 ± 3.69 ($t=-4.22$ $p<0.01$), at six months weight increased again to 26.3 ± 3.49 ($t=-5.08$ $p<0.01$) and at twelve months post-transplant, the mean BMI was significantly higher at 27.1 ± 4.6 ($t=-3.02$ $p<0.01$). This is equivalent to a mean weight gain of 7.8 ± 7.42 kilograms from pre-transplant to twelve months post-transplantation. Significant changes in weight were not evident again after this time. Figure 4.5 represents this data.

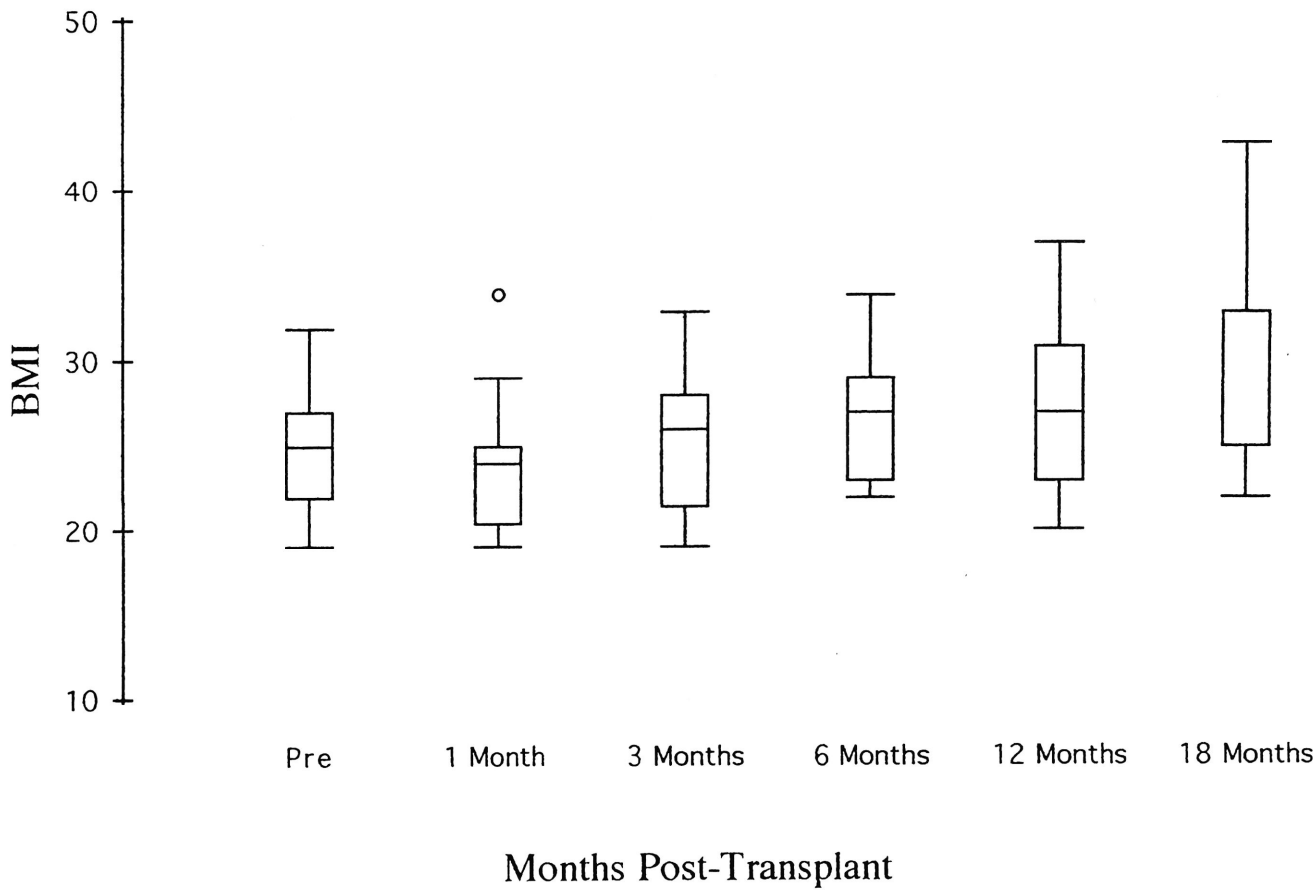


Figure 4.5: Changes in body mass index (BMI) over time in cardiac transplant recipients

To determine any differences between post-transplant body weight and weight prior to the onset of cardiac failure, participants ranked their present weight as increased, decreased or no change when compared to pre-transplant *usual* weight. Seventy per cent of patients indicated that their weight had increased, 11 per cent said it had decreased and 19 per cent reported that their current weight was comparable to healthy pre-transplant weight. Refer to Table 4.3 below.

Weight change	***Percentage***
No Change	19 %
Increased	70%
Decreased	11%

Table 4.3: Self-reported changes in usual weight following cardiac transplantation

4.4 Body Fat Distribution

Indicators of body fat distribution were measured at the time of participation in the study. These included waist-to-hip ratio (WHR) and waist circumference. A WHR exceeding 0.90 for males, 0.80 for females and a waist circumference greater than 100 cm were considered to pose cardiovascular risk. The mean WHR for males was 1.01 ± 0.06. A t-test revealed that this was significantly higher than recommended ($t=8.713$ $p<0.01$). The mean WHR of 0.80 ± 0.06 for females did not indicate cardiovascular risk. Overall, 88 per cent of the total transplant population displayed a WHR larger than desirable. The mean waist circumference was 100.7 ± 15.7 cm and 33 per cent of participants had a circumference measure greater than 100 cm. Table 4.4 below shows the mean, range and t-test values for these variables.

Variable	*Mean± SD*	*Range*	*Recom.*	*P Value*
Waist Circumference	100.7 ± 15.7	85.0 - 132.5	< 100 cm	NS
Waist-to-Hip Ratio				
Males (N= 23)	1.01 ± 0.06	0.94 - 1.10	< 0.90	p<0.01
Females (N=4)	0.80 ± 0.06	0.75 - 0.89	< 0.80	NS

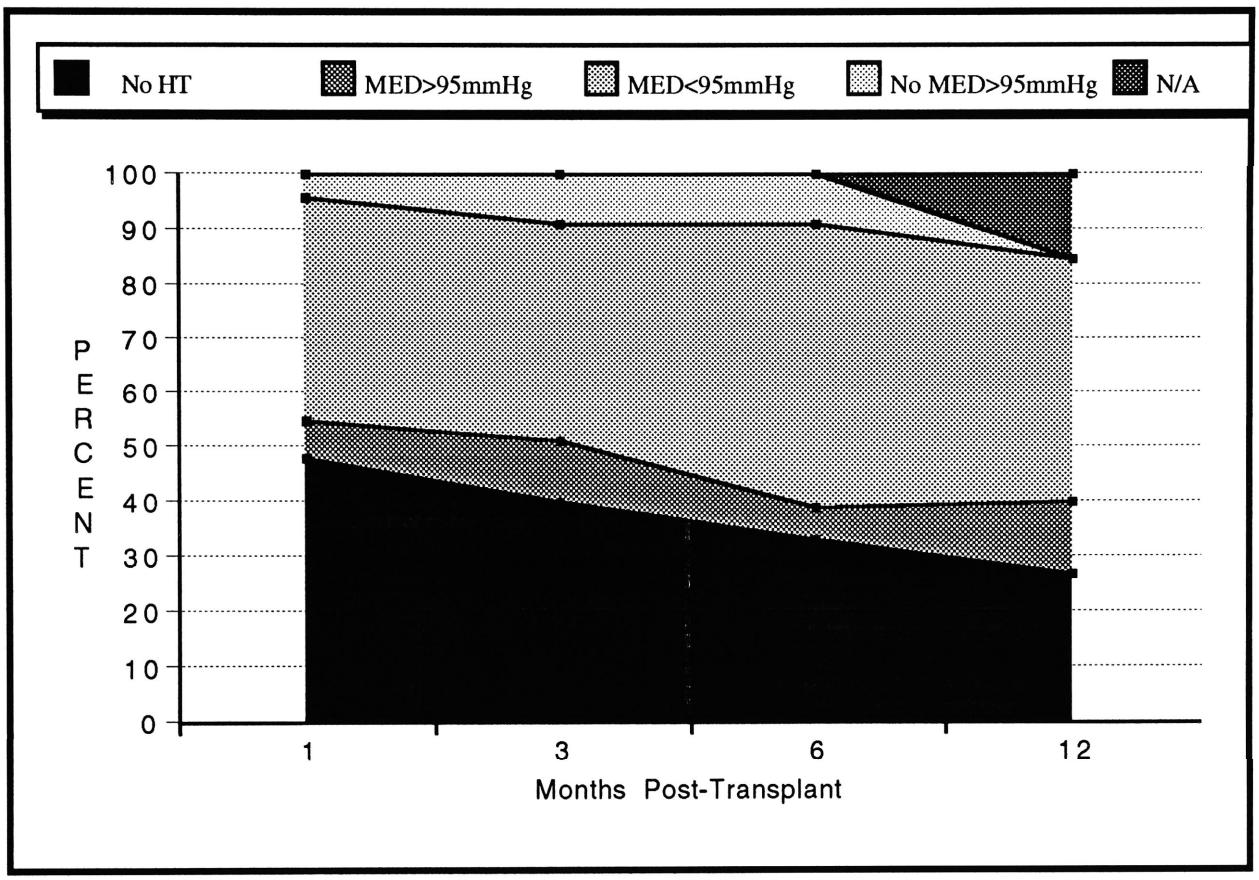
Table 4.4: Indicators of body fat distribution in male and female cardiac transplant recipients

4.5 Diabetes Mellitus

Post-transplant diabetes mellitus occurred in five (19%) of the twenty seven participants. Two participants (7%) also exhibited non-insulin dependant diabetes mellitus prior to transplantation which was evident in the post-operative period. Two of the patients were maintained on insulin, whilst the remaining five were controlled with sulphonylurea oral hypoglycaemia agents.

4.6 Blood Pressure

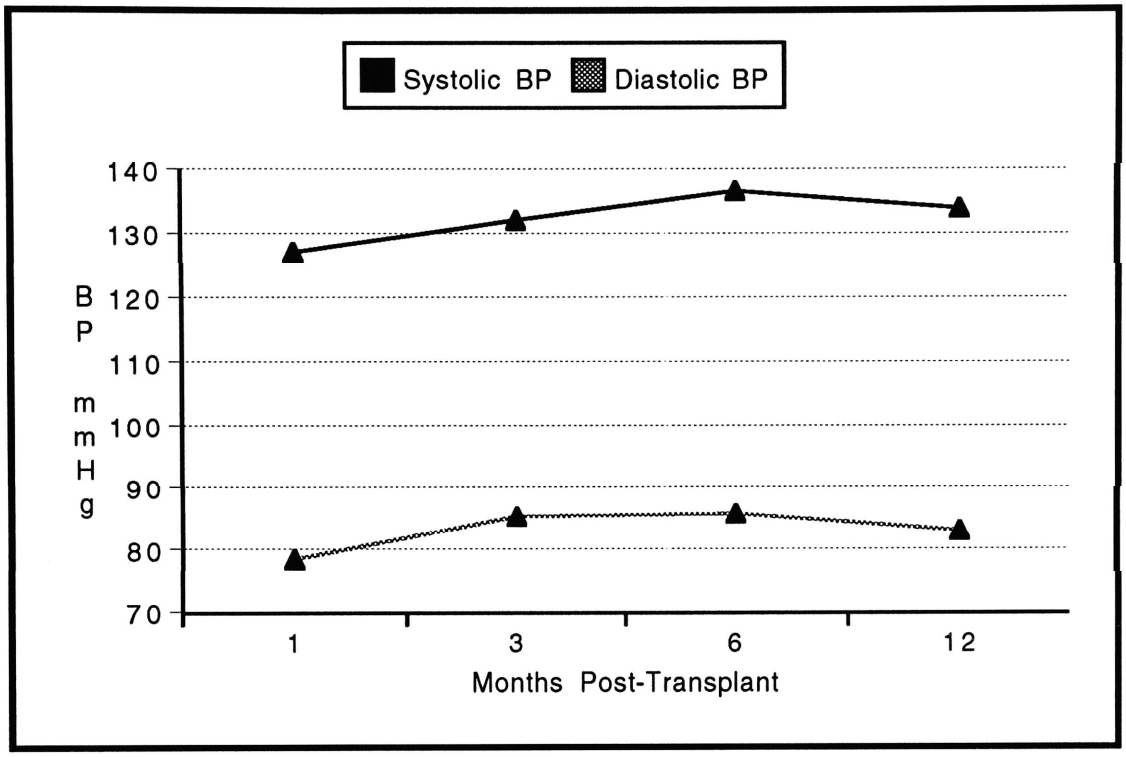
Hypertension was determined as a blood pressure exceeding 95 mmHg diastole or the administration of anti-hypertensive medications. At one month post-operative, 52 per cent of participants displayed hypertension. This increased to 60, 67 and 73 per cent at three, six and twelve months respectively. This is shown in figure 4.7 below.



4.6 Hypertension over time following cardiac transplantation

Mean diastolic and systolic blood pressures for the post-transplant population are shown in figure 4.7. Blood pressure over time did not change significantly with an analysis of variance (ANOVA). At one month post-operative mean blood pressure for the group was

79 / 127 mmHg. At three, six and 12 months these values were 85 / 132, 86 / 137 and 83 / 134 mmHg respectively. Over time following transplantation, none of the transplant recipients displayed persistent uncontrolled hypertension.



4.7 Changes in mean blood pressure over time following cardiac transplantation

4.7 Dietary Intake

All heart transplant recipients had been seen by a dietitian in the post-operative period. Table 4.5 below shows the mean dietary intakes of total fat, saturated fat, protein, carbohydrate, fibre, cholesterol and sodium. A t-test was performed to compare nutrient intakes with current recommendations.

Nutrient	*Mean + SD*	*Recom.*	*PValue*
Fat (% energy)	31.7 ± 4.73	< 30%	<0.05
Saturated Fat (% energy)	11.1 ± 3.01	< 10%	<0.05
Carbohydrate (% energy)	41.5 ± 7.31	55 - 60%	<0.01
Protein (% energy)	21.8 ± 3.78	15 - 20%	<0.01
Cholesterol (milligrams)	317 ± 157.0	< 300 mg	NS
Fibre (grams)	31.1 ± 10.1	25 - 30 g	-
Sodium (mmol)	121.9 ± 36.5	40 - 100 mmol	<0.01

Table 4.5: Dietary intake of cardiac transplant recipients compared to recommendations

Fat

The mean intake of total fat was significantly higher than the current dietary recommendations ($t=1.84$ $p<0.05$). There was considerable variability in regards to fat intake. A low fat diet was considered to be <30 per cent contribution to energy, a moderate fat diet was between 30 to 35 per cent of energy and a high fat diet was at intakes above this level. The percentage of patients with low, moderate and high fat intakes was 37, 37 and 26 per cent respectively. The range of fat intakes is shown in figure 4.8 below.

Saturated Fat

The mean intake of saturated fat was 11.1 ± 3.01 grams per day. This was significantly higher than the currently recommended < 10% of energy ($p< 0.05$). Figure 4.8 shows the range of saturated fat intakes in transplant recipients. A low intake was regarded to be <10 per cent of energy as recommended, a moderate was from 10 to 15 per cent of energy and a high at intakes above this level. Thirty seven, 56 and 7 per cent of recipients respectively displayed intakes at these levels.

Carbohydrate

The mean carbohydrate intake of the transplant population was significantly lower than the currently recommended 55 to 60 per cent of energy ($t=-9.78$ $p<0.01$). The range of carbohydrate intakes is shown in figure 4.8 below. A low carbohydrate intake of <40 per cent of energy was demonstrated in 44 per cent of transplant recipients. A moderate intake of 40 to 55 per cent of energy was found in 56 per cent of participants whilst no participants had a high carbohydrate intake (>55 per cent of energy) as recommended.

Protein

Protein intake of the transplant population contributed to a mean 21.8 per cent of total energy. This was significantly higher than the recommended 15 to 20 per cent contribution of protein to energy intake ($t=2.50$ $p<0.01$). The range of protein intakes is

shown in figure 4.8 below. A low protein was regarded as <20 per cent of energy. This was demonstrated in 26 per cent of participants. Moderate intakes of 20 to 25 per cent of energy were found in 52 per cent, whilst 22 per cent displayed high intakes of >25 per cent of energy.

Cholesterol

The mean cholesterol intake for the heart transplant population was 317 mg per day. This was higher than the currently recommended 300 mg daily. However, the difference was not statistically significant. Cholesterol intake was rated as low, <300 milligrams (as recommended), moderate, 300 to 400 milligrams and high >400 milligrams daily. Low, moderate and high cholesterol intakes were found in 55, 30 and 15 per cent of participants respectively. Refer to figure 4.8.

Fibre

The mean fibre intake for the heart transplant population was 31.1 gram per day. This level meets the current recommendations for fibre. The range of fibre intakes, low (<20 grams), moderate (20 - 30 grams) and high (>30 grams) were found in eight, 44 and 48 per cent of participants respectively. This is shown in figure 4.8.

Sodium

The mean sodium intake for this population was 121.9 mmol daily. This was significantly higher than the currently recommended 40 to 100 mmol per day ($t=2.82$ $p<0.01$). The range of intakes is shown in figure 4.8. A low intake was considered to be <100 mmol as recommended, this was evident in 29 per cent of transplant recipients. A moderate intake of 100 to 150 mmol was reported by 52 per cent, whilst intakes above this level were evident in 19 per cent of participants. Figure 4.8 shows these results. The salt (sodium chloride) avoidance practices of transplant recipients were also noted in the study. Table salt use was reported by 15 per cent of participants, the use of salt in cooking by 11 per cent and both practices by 7 per cent of transplant recipients.

Alcohol

Alcohol intake was classified as low, moderate or high risk based on *National Heart Foundation* guidelines (refer to appendix 11.5). Thirty seven per cent of transplant recipients reported that they were non-drinkers, the remaining 63 per cent were classified as low risk for alcohol intake. Refer to figure 4.8.

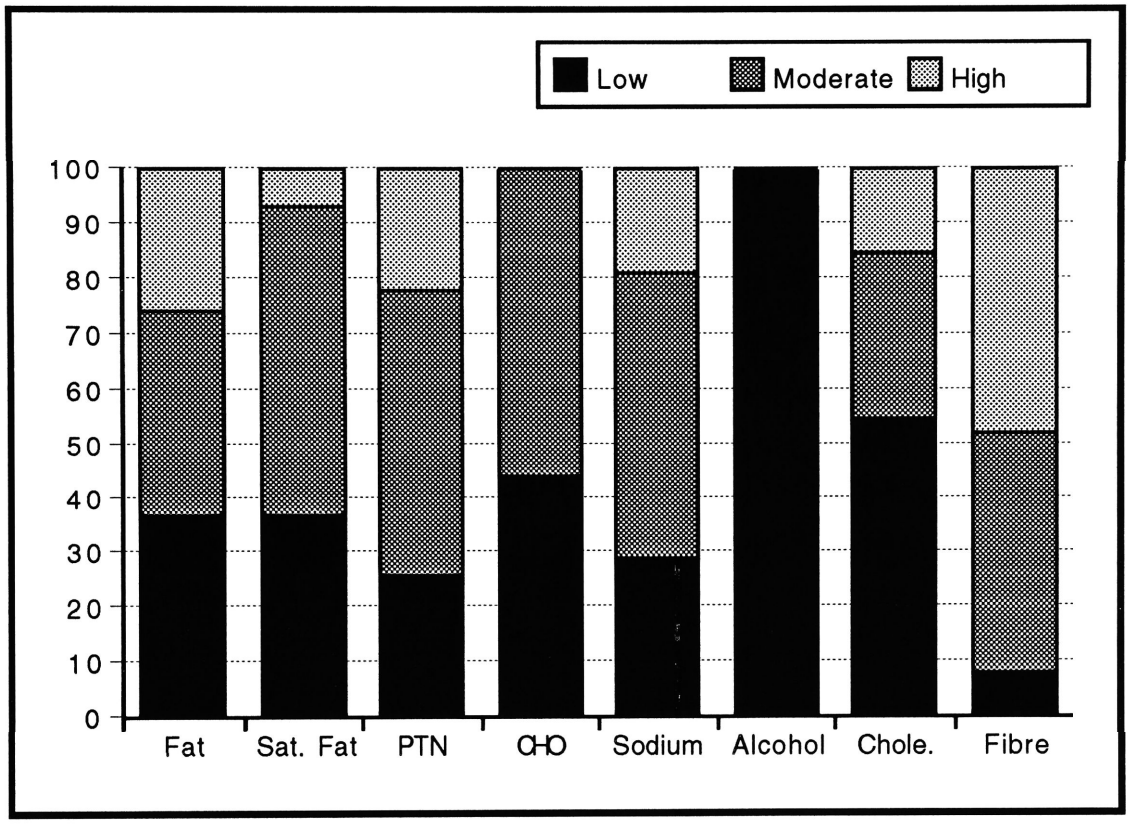


Figure 4.8: Classifications of dietary intake for selected nutrients in the post-cardiac transplant population

Current Eating Pattern

Seventy one per cent of heart transplant recipients said that they were currently following some kind of special diet. A low fat diet was the most frequent, followed by a reduced fat and salt diet. These results are presented in table 4.6 below.

Diet	*Percent*
No special diet	29%
Reduced fat	29%
Reduced fat / salt	22%
Diabetes Diet	10%
Healthy Diet	10%

Table 4.6: The usual eating behaviour described by cardiac transplant recipients

Exercise

Participants described exercise habits in terms of frequency, intensity and type of activity. At 12 to 24 months post-transplant, only 48 per cent of cardiac transplant recipients were exercising at the recommended level of 30 minutes duration, three times per week. The remaining participants were either exercising at a level below this or were sedentary.

Appetite

To determine possible factors which may influence dietary intake, participants were asked to rate their current appetite and any changes in appetite since transplantation. The majority of participants reported that their current appetite was excellent and that appetite had increased following transplantation These results are described in Table 4.7 and 4.8.

Current Appetite	*Per cent*
Poor	4%
Good	37%
Excellent	59%

Table 4.7: Appetite at 12 - 24 months post-transplant as described by cardiac transplant recipients

Appetite Changes	*Per cent*
Increased	81%
Decreased	11%
No Change	8%

Table 4.8: Self reported changes in appetite following cardiac transplantation

5. DISCUSSION

Heart transplant recipients are faced with CAD as an ironic impediment to long term survival. Conventional cardiovascular risk factors potentially contribute to this disorder. This study was initiated to describe the cardiovascular profile of a healthy post-cardiac transplant population. Dietary intake was investigated to further describe cardiovascular risk and identify adherence with current nutritional recommendations.

5.1 Lipid Levels

Previous studies have demonstrated that elevations in plasma lipids occur frequently following cardiac transplantation and that these are strongly related to CAD development (Winters et al 1990; Barbir et al 1991; Eich et al 1991). In the present study, 41 per cent of transplant recipients displayed hyperlipidaemia at twelve months post-transplant, as evident by the administration of lipid lowering drugs or cholesterol / triglyceride levels above desirable ranges. The prevalence of lipid abnormalities in this study is lower than that suggested by other researchers. Rudas et al (1990) for example, reported that 83 per cent of cardiac transplant recipients manifested hypercholesterolaemia by one year post-transplant. Similarly, Keogh et al (1988) found that 50 per cent of transplant recipients with underlying ischaemic heart disease and 33 per cent of those with diagnosed non-ischaemic cardiomyopathy displayed cholesterol elevations beyond desirable levels. These inconsistencies can be attributed to several key differences in the research. Firstly, differing definitions of lipid elevations have been used by investigators. Rudas et al (1990) for example, used total cholesterol levels >5.2 mmol/ L to describe lipid elevations. Whilst Keogh et al (1988) considered a significant degree of hypercholesterolaemia to be total cholesterol >6.5 mmol/L. In this study, hyperlipidaemia was described as total cholesterol greater than 5.5 mmol/L or triglycerides >1.8 mmol/L. As a result of these varying definitions, the prevalence rates show obvious differences. In addition, differences in medication protocols between

study populations (particularly lipid lowering agents), differences in sample sizes and the timing of post-transplant blood lipid measurements are likely to influence results.

The prevalence of lipid abnormalities in this group is comparable to those found in the general population. The *National Heart Foundation Risk Factor Prevalence Survey* (1989) demonstrated that 47 per cent of males and 39 per cent of females had cholesterol levels exceeding 5.5 mmol/L. Whilst 17 per cent of males and 7 per cent of females had triglyceride concentrations of greater than 2.0 mmol/L. On the surface this may suggest that the cardiac transplant population are in fact no different from the Australian population in terms of this cardiovascular risk factor. However, considering the accelerated rate at which CAD often appears in transplant recipients and a primary background of cardiovascular complications, these patients are possibly at greater cardiovascular risk due to lipid elevations than the general population. Hence, cholesterol levels above desirable should be treated aggressively in the post-transplant period.

The pattern of lipid abnormalities demonstrated in this study suggests that hyperlipidaemia develops immediately following cardiac transplantation. The development of serum cholesterol elevations occurred within the first three months post-transplant. After this time and up to twelve months post-transplant, cholesterol levels remained at the currently recommended levels or slightly elevated. Other studies have demonstrated a similar time course for hypercholesterolaemia. Both Stamler et al (1988) and Rudas et al (1990) found that total cholesterol elevations reached statistical significance at three months post-transplantation. After this time, some investigators have found that blood lipids continue to increase (Ballantyne et al 1987), whilst others, like that found in this study, have demonstrated that these biochemical indicators remain elevated throughout the post-transplant period without further significant increases (Becker et al 1988; Stamler et al 1988).

Serial evaluations of triglyceride levels in this study showed a similar pattern of post-transplant elevation. Inconsistencies in the availability of data however, did not allow for statistical analyses. Despite this, a trend towards triglyceride elevations was evident from three months following transplantation, suggesting that this population show some characteristics of hypertriglyceridaemia. Other studies have confirmed that this lipid abnormality is evident following cardiac transplantation (Becker et al 1987; Keogh et al 1988). However, in the present study, a high prevalence of hypertriglyceridaemia may not have been evident because of the small sample size, missing data and the selection of patients with normal liver and renal function.

Although lipid elevations were determined to be significant at three months post-transplant, it is important to recognise that in the present study, pre-transplant blood lipid levels were analysed at end-stage cardiac failure. Hence, blood lipids may have been artificially depressed by myocardial infarction, cardiac cachexia, elevated catecholamines and changes in gastrointestinal absorption, even in patients with known pre-transplant hyperlipidaemia and ischaemic heart disease (Ballantyne et al 1987). Pre-morbid lipid values would therefore provide a more valid comparison of pre versus post-transplant lipid elevations. Despite this, it is still notable that the mean three month post-operative cholesterol level of 6.1 ± 1.6 mmol/L is above the recommended range for total cholesterol, indicating that hypercholesterolaemia is an issue for the heart transplant population immediately post-transplant.

Data on changes in lipoprotein cholesterol following cardiac transplantation were not available for analysis in this study. Other researchers have demonstrated that the lipoprotein profile of this population tends to be particularly atherogenic. Stamler et al (1988) demonstrated that LDL cholesterol elevations were evident from two weeks following cardiac transplantation. The total cholesterol to HDL cholesterol ratio which correlates with cardiovascular risk was also found to increase throughout the first post-transplant year. Other researchers have also reported transient increases in HDL

cholesterol levels, however, these appear to stabilise within the first three months post-transplant (Becker et al 1988; Ballantyne et al 1992). Although cholesterol sub-fractions were not reported in the present study, it is likely that the pattern of lipoprotein changes demonstrated by other researchers was similar for this population.

The development of hyperlipidaemia in this population could be the result of a number of factors. Other researchers have shown that obesity is strongly associated with lipid elevations (Keogh et al 1988; Rudas et al 1990). Considering the high prevalence of overweight and obesity in this population, this is a potential contributing factor. The use of immunosuppressive medications may have played a role in this disorder, as all participants were receiving triple drug immunosuppression with cyclosporine, azathioprine and prednisone. Prednisone alone has been shown to elevate cholesterol and triglyceride levels by up to 10 and 20 per cent respectively (Bagdale et al 1970). The establishment of low maintenance doses of immunosuppressants may also explain the stabilisation of lipid values seen up to 12 months post-transplant. The administration of anti-hypertensive medications which in renal transplant patients has been associated with hyperlipidaemia (Vathsala et al 1989) was also frequent in this population. It is also possible that diet contributed to hyperlipidaemia, as the dietary intakes of fat and saturated fat were greater than desirable in a considerable proportion of patients. This is strongly associated with total cholesterol elevations (Kromhout et al 1989). In addition, physical activity, which has benefits for lipid profile including reductions in LDL cholesterol, was generally low for this population.

Overall, the results of this study suggest that hyperlipidaemia is a cardiovascular risk factor which develops in a considerable proportion of transplant recipients following cardiac transplantation. It appears that this anomaly is particularly a problem during the first three months post-transplant. Considering the predisposition to cardiovascular problems in this population and the negative implications of hyperlipidaemia for CAD development, close monitoring and tight control of blood lipid levels through

pharmacological, dietary or lifestyle intervention may be beneficial to the cardiovascular health of this population.

5.2 Body Weight

Weight gain following cardiac transplantation has the potential to influence the establishment of other cardiovascular risk factors and possibly influence CAD development. The prevalence of overweight (BMI >25) in this population was 56 per cent at 12 months following transplantation. At the same time, one third of these patients were classified as obese (BMI >30). The findings of Grady and Herold (1988) suggest similar prevalence rates, with 51 per cent of transplant patients in their study population being overweight at six months following transplantation. This compares with more recent studies on post-transplant obesity by Lake et al (1993) who reported a 39 per cent prevalence of overweight at 12 months post-transplant, suggesting that weight gain appears to more widespread in the present study population. This variance may be due to an actual difference in weight gain in this study population or possibly be the result of difference in sample size or classifications of overweight and obesity.

The temporal sequence of body weight changes in this study was an initial decrease in mean BMI from 24.7 pre-transplant to 23.9 ($p<0.01$) at one month post-transplant. This immediate post-transplant weight loss could be attributed to an acute post-surgical phase, infection or early rejection (Kumar and Coulston 1983). Alternatively, it is possible that significant decreases in mean weight did not actually occur, as pre-transplant weights were recorded at initial assessment for cardiac transplantation, often several months before transplant procedures. As a result, patients may have weighed less immediate pre-transplant and at one month may have had similar body weights. Because cardiac transplantation is an emergency procedure and reliant on the availability of donor hearts, data on pre-transplant body weight at a comparable points in time for each recipient is not obtainable.

Following immediate post-transplant weight loss, body weight increased progressively up to 12 months post-transplant with significant gains between each increment ($p<0.01$). The mean weight gain at 12 months from baseline was 7.8 kilograms in this study population. These findings are comparable to those reported by several other researchers. Grady and Herold (1988) demonstrated a mean weight gain of 7.4 kilograms at six months post-transplant. Further changes in weight were not reported after this time. Hagan et al (1990) reported a slightly higher increase of 8.7 kilograms at one year in transplant patients maintained on corticosteroid therapy. In comparison, Keogh (1988) who undertook a previous study on the St. Vincent's Hospital transplant population reported a mean weight gain of 4 kilograms at 12 months after cardiac transplantation. The findings of a mean 12 month weight gain of 7.8 kilograms in the present study suggest that Keogh's recommendations for more stringent efforts at weight control have not been adequately implemented. In addition to this, patients self-assessments of their own body weight suggests that weight not only returns to pre-morbid levels, but in a large number of transplant recipients, actually exceeds pre-transplant usual weight. As a result, the degree of weight gain in this group of patients may not only be unacceptable in terms of reference standards, but also exceed the patients own previously set-point for body weight.

Although these findings suggest that body weight increases over time following cardiac transplantation, several factors which affect the accuracy of these results must be considered. Firstly, information regarding body weight was obtained from St. Vincent's Hospital medical records and not measured directly by the researcher. As a result, measurements were taken by a number of hospital staff and to differing degrees of precision (eg. 1.0 kg versus 0.25 kg). Also, height was obtained from pre-transplant records and although this was verbally confirmed with participants, it is not known if transplant patients were actually measured to obtain this data. In addition, the presence of oedema in this population, which occurs as a result of prednisone therapy may have potentially influenced any measures of body weight in this study. Finally, participants

self-assessment of changes in body weight following transplantation may have been skewed by the fact that many were ill for a long period prior to the availability of a suitable donor heart. As a result, usual or healthy body weight may have been under-estimated.

Evidence suggests that the distribution of body fat is predictive of cardiovascular risk in the non-transplant population (Donahue et al 1987; Ducimetiere and Richard 1989; Hartz et al 1990). Although this has yet to be investigated in cardiac transplant recipients, it is likely that the presence of abdominal or android obesity has similar metabolic and cardiovascular complications for this population. Prior studies on the body composition of cardiac transplant patients have suggested that percentage body fat is increased and muscle mass is reduced (Ketayian et al 1992). However, the pattern of fat distribution in this population remains largely undescribed. One previous study undertaken with renal transplant recipients suggested that fat redistribution, as associated with immunosuppressive therapy in transplant patients was not evident (Horber et al 1986). In comparison to this, the findings of the present study which utilised the WHR and waist circumference suggested that an abdominal pattern of fat distribution was frequent in the post-transplant population. Eighty eight per cent of transplant recipients had WHR greater than recommended, whilst 33 per cent had a waist circumference in excess of 100 centimetres. These indices suggest that abdominal obesity poses considerable cardiovascular risk to the transplant population.

The limitations of the chosen methodology, however must be considered before making any conclusions regarding the body fat distribution of the transplant population. Other researchers have suggested that WHR may not be predictive of cardiovascular risk in individuals with a small hip circumference (Despres et al 1990). Measurements of the WHR also fail to distinguish visceral metabolically active fat from subcutaneous abdominal fat (Ross et al 1992). Whilst, in obese patients, difficulties in identifying measurements sites reduce the accuracy of the results. Further research into body fat

distribution utilising other assessment techniques may provide more insight into the cardiovascular profile of this population.

When compared to measures of overweight and obesity in the Australian population, the post-cardiac transplant population display a tendency towards higher mean body weights and waist circumferences. The mean BMI of men and women reported by the *National Heart Foundation* (1989) was 25.3 and 24.3 respectively. In comparison, the mean 12 month post-transplant BMI in this population was high at 27.1. Additionally, the average waist circumference of 100.7 cm demonstrated in this study is considerably greater than the 89 cm for men and 76 cm for women reported by the *National Heart Foundation.* This evidence suggests that the transplant population may be at increased cardiovascular risk in regards to body weight than the general population.

The cause of post-transplant weight gain in this population is most likely multi-factorial. Steroid administration however, appears to play a significant role. Other researchers have demonstrated that transplant recipients maintained on steroids, gain significantly more weight than those undertaking corticosteroid free maintenance therapy (Hagan et al 1990). The mechanism for this effect has been largely related to steroid induced appetite changes. In this study, 59 per cent of recipients reported that their present appetite (at 12 to 24 months post-transplant) was excellent, while only 4 per cent suggested that appetite was poor. Poor appetite seemed to appear in patients who were ill at the time of the study or taking appetite altering medications. The majority of post-transplant recipients (81 per cent) also reported that their appetite had increased over the post-transplant period. As a result of altered appetite patients may exhibit energy intake in excess of physiological requirements, of which weight gain is the result. In addition to the adverse effects on appetite, steroids have also been shown to stimulate changes in body composition (Schneider et al 1977). Increased truncal or abdominal fat tends to be the result. Steroid administration in the present patients population may therefore also act to explain the high prevalence of abdominal obesity.

A history of pre-transplant obesity has also been suggested to predict the development of overweight and obesity following cardiac transplantation (Hagan et al 1990; Lake et al 1993). The present study confirmed this. At 12 months post-transplant, nine of the participants in this study were obese (BMI >30). Retrospective analysis of weight records revealed that all of these patients were actually overweight (BMI >25) prior to transplantation. As a result, close monitoring of patients displaying a pre-transplant weight above desirable or with a history of overweight may assist in reducing the prevalence of this long-term complication of cardiac transplantation.

Physical inactivity may also enhance weight gain in this population. Over a half of the transplant population were either exercising below the currently recommended 30 minutes, three times per week or sedentary in their activity level. The combined effect of corticosteroids and physical inactivity, superimposed on a history of obesity may therefore contribute to the increased body weight seen in this group of patients following cardiac transplantation.

The adverse implications of excessive weight gain in the transplant population are multiple. Overweight and obesity have been associated with elevations in total cholesterol, LDL cholesterol, triglycerides and reduced HDL cholesterol levels (Bonora et al 1991). Several studies have confirmed that weight gain is a key factor in lipid elevations in transplant recipients (Keogh et al 1988). The development of post-transplant diabetes mellitus may also be related to some extent to weight changes (Hagan et al 1990), although has not been adequately investigated in this population, to date. Furthermore, inappropriate weight gain has been shown to exacerbate hypertension and adversely affect cardiac functioning, which in the long term may have deleterious effects on the integrity of the transplanted heart (Hagan et al 1990).

Although weight gain is a concern for the cardiovascular health of the majority of transplant recipients, in a small number of patients weight gain in the post-transplant

period may actually be beneficial. At one month post-transplant, five transplant recipients were below the healthy weight range as indicated by a BMI <20. Increases in weight, particularly fat free mass to achieve a weight appropriate to height, is therefore desirable for this sub-group of transplant recipients.

The present study provides considerable evidence that body weight increases over time following cardiac transplantation. In general, this group of patients are inclined to be overweight with an android pattern of fat distribution, which indicates that they have a high risk profile for CAD development. Measures to alleviate this clinical problem would therefore be beneficial. It is possible that aggressive cardiac rehabilitation, pre-transplant weight reduction (in obese patients) and patient education may be a means of addressing the weight control issue. Whilst there is some evidence that behavioural techniques may achieve sustained weight reduction in this population (Robert et al 1990). Ultimately, the most appropriate intervention for attaining and maintaining a healthy body weight would be individualised, implemented early post-transplant and take into account the myriad of factors which impact upon the weight status of cardiac transplant recipients.

5.3 Diabetes Mellitus

Post-transplant diabetes mellitus is a significant long-term complication of cardiac transplantation. The prevalence of this disorder has been reported to vary from 8 to 14 per cent depending on the definition used (Utresky et al 1987; Ladowski et al 1989). In the present study, a total of seven post-cardiac transplant patients displayed diabetes in the post-transplant period. Of these, two had diabetes prior to transplantation and the remaining five developed this complication in the post-transplant period. The resultant prevalence of post-transplant diabetes mellitus was therefore 19 per cent. Of these patients, two were maintained on insulin and the remaining five on oral hypoglycaemic agents.

In the patient population studied for this research, blood glucose levels were not regularly available for analysis. Detection of diabetes mellitus in this population therefore tended to occur symptomatically, rather than early in the post-transplant period. It is plausible therefore, that a considerable proportion of these patients have undiagnosed diabetes mellitus. As a result, the actual prevalence rates for diabetes following cardiac transplantation would be much higher. The irregular blood glucose monitoring of these patients also failed to allow for any analysis of diabetic control or detection of the temporal sequence of diabetes development in this population.

The underlying cause of diabetes mellitus in this population is likely to be the combined effect of immunosuppressive administration and post-transplant weight gain. Steroids are thought to induce diabetes via the effects on peripheral insulin resistance and impaired glucose tolerance (Gardiner 1993). Cyclosporine on the other hand has been linked to similar metabolic changes, however this has yet to be demonstrated in this patient population. In this study, all transplant recipients were receiving both corticosteroids and cyclosporine. Weight gain, as common in this population, also corresponds to the development of insulin resistance and in the long term, decompensation of pancreatic function (Thomas 1994). As a result diabetes may have developed in a number of these patients as a result of inappropriate weight gain over the post-transplant period.

In the present study, it was difficult to make any valid conclusions regarding post-transplant diabetes mellitus, because of the limited amount of available data. Despite this, it is evident that the presence of diabetes mellitus in this population is likely to have negative implications for cardiovascular profile. As a result, early diagnosis, weight control and appropriate dietary intervention would be beneficial to this patient population.

5.4 Blood Pressure

Hypertension is a significant complication of cardiac transplantation that has been reported to affect up to 90 per cent of all post-transplant recipients (Radovancevic et al 1990; Renuld et al 1989). Although blood pressure elevations have not been unequivocally linked to post-transplant CAD, there is some evidence that this may be a contributing risk factor to the development of this disorder (Winters et al 1990; Radovancevic et al 1990). In this study, hypertension as defined by a diastolic blood pressure >95 mmHg or the administration of anti-hypertensive medications, was evident in 73 per cent of long-term transplant recipients. It is possible that the prevalence in this study was actually lower than that reported by other researchers because of the small sample size, the exclusion of patients with diagnosed renal impairment or the definition of hypertension used.

Over time the development of hypertension tended to become more prevalent. Immediately post-transplant only 52 per cent of transplant recipients displayed this disorder. By six months post-transplant the prevalence of hypertension reached 67 per cent and by 12 months 73 per cent of this population were hypertensive. Although hypertension appears to be a frequent complication of transplantation, blood pressure was generally maintained within recommended limits in this group of patients. The mean diastolic blood pressure at 12 months post-transplant was 84 mmHg, whilst systolic blood pressure averaged at 134 mmHg. In the present study, none of the transplant recipients displayed persistent uncontrolled hypertension. It is likely that this is the result of close monitoring and pharmacological intervention in the post-transplant period. Although it is plausible that these results reflect the fact that blood pressure was measured only once at each point in time. Since the requirements for a diagnosis of hypertension require blood pressure elevations from consecutive readings, it is possible that blood pressure control or the prevalence of hypertension therefore, actually differed from these findings. However, in theory, if blood pressure is as well controlled as indicated by this

study, complications for cardiac function and CAD development are likely to be minimised.

In comparison to data from the Australian population, evidence from this study suggests that transplant recipients are considerable different from the general population in regards to the development of this disorder. Population studies, using the same blood pressure classifications as used in the present study, suggest that hypertension is present in 17 per cent of men and 13 per cent of women (National Heart Foundation 1989). The 73 per cent prevalence rate for hypertension in this study therefore indicates that other factors clearly play a role in this disorder. Despite this, the degree of blood pressure control was relatively similar to population levels.

The underlying cause of hypertension in cardiac transplant patients has been most strongly related to cyclosporine administration (Myers et al 1984; Martin et al 1987). In this study, all patients were receiving immunosuppression with this medication over the post-transplant period, suggesting it as a probable underlying factor. However, the frequent development of blood pressure elevations in the pre-cyclosporine era of cardiac transplantation has suggested that other factors may contribute to this disorder (Ozdogan et al 1990). It is possible that blood pressure increased in response to post-transplant induced physiological changes (Shapiro et al 1990). This could not be examined in this study. Prednisone has also been implied as a causative factor. However in the present study, the prevalence of hypertension increased over time, whilst steroid administration was reduced. Hence this relationship is unlikely. Alternatively, weight gain which correspondingly increased over time with elevations in blood pressure may act to explain the prevalence of this disorder. This hypothesis is supported by evidence from non-transplant populations which has strongly linked weight gain to elevations in blood pressure (Havlik et al 1983).

Although blood pressure was on the whole, well controlled in this population, it could be hypothesised that a combination of weight reduction, sodium restriction and lifestyle modifications (eg. smoking cessation, physical activity) may alleviate the need for pharmacological treatment of this disorder. Although this has been demonstrated to be the case in the general population (Elmer et al 1991), few intervention studies including heart transplant recipients have been reported to date. However, until these studies provide more of an insight into possible treatment alternatives for this disorder, frequent monitoring and control of blood pressure, as is currently being implemented, should continue for these patients. Whilst non-pharmacological interventions should be encouraged as a complementary CAD preventative measure.

5.5 Dietary Intake

The goal of long-term nutritional therapy for the heart transplant recipient includes achieving reductions in total fat, saturated fat, cholesterol, alcohol and sodium, whilst increasing intakes of carbohydrate and dietary fibre (Frazier et al 1985). Although the efficacy of such a healthy heart diet in improving the cardiovascular profile of cardiac transplant recipients has not been widely reported, evidence from some researchers suggests that dietary modifications may positively influence blood lipids, blood pressure and body weight (Salen et al 1994; Singer et al 1994). In the present study, the intake of each of these dietary components was analysed for all participants using an extensive diet history.

Fat intake is one dietary component which has implications for plasma lipids, lipoproteins and body weight. As a result, a high fat diet has been associated with an increased risk of cardiovascular diseases (Shrapnel et al 1992). In the present study, the fat intake of long-term cardiac transplant recipients contributed a mean 31.7 per cent of energy to the diet. This was significantly higher than the recommended <30 per cent of energy ($p<0.05$), however less than the average intake reported for the Australian population (Lester 1994). Thirty seven per cent of transplant recipients met the current

recommendations for total fat intake and 26 per cent actually had a fat intake >35 per cent of energy. It is interesting to note however, that 51 per cent of transplant recipients indicated that they were following a diet which included reductions in total fat content. This suggests possible inaccuracies in dietary analysis or discrepancies between participants perceptions of what constitutes reductions in dietary fat and an actual low fat diet. Consequently, recommendations for reducing total fat intake and the means by which this can be achieved should be reinforced in the cardiac transplant population.

The saturated fat intake of this population was also significantly higher than current recommendations ($p<0.05$). The mean intake of saturated fat 11.1 per cent of energy, whilst that which is recommended is less than 10 per cent of energy. Only one third of transplant recipients were currently consuming a saturated fat intake as desired. Reducing the saturated fat content of the diets of transplant recipients is therefore recommended. Salen et al (1994) provided evidence that such a dietary modification may be advantageous for the cardiovascular profile of this population, reducing both total cholesterol and LDL cholesterol levels.

The cholesterol intake of this group of patients was also assessed in the present study. The mean cholesterol intake of 317 milligrams per day did not differ significantly from the maximum 300 milligrams per day as desired. Most participants in this study had low to moderate cholesterol intakes with only a small group of recipients greatly exceeding recommendations. Overall, this suggests that transplant recipients generally adhere to low cholesterol dietary recommendations which may be beneficial to cardiovascular profile.

Alcohol is considered to pose cardiovascular risk at high levels of consumption (Ahlawat and Siwach 1994). In this study, 37 per cent of cardiac transplant patients were non-drinkers. The remaining 63 per cent reported low alcohol intake. Hence cardiovascular risk in terms of frequency and quantity of alcohol consumed was low for this population.

In heart transplant recipients sodium restriction is recommended for blood pressure control and to eliminate the presence of oedema caused by steroid administration (Kumar and Coulston 1983). Previous studies on the cardiac transplant population have shown that blood pressure is sensitive to reduced sodium intake and that extremely low sodium diets can result in large decreases in systolic blood pressure (Singer et al 1994). Extrapolating these results, it is possible that a sodium intake at the recommended level of 40 to 100 mmol per day can achieve modest blood pressure reductions. In this study, dietary analysis revealed that the mean sodium intake of this population was 121.9 mmol per day and that 71 per cent of transplant recipients had sodium intakes greater than recommended. It was also interesting to note that only a small proportion of transplant recipients actually reported the addition of salt to their diets, suggesting that sodium intake was obtained from other dietary sources. Hence, there is room for dietary intervention to reduce the sodium intake of this group of patients.

An adjunct to the recommended low fat intakes for a healthy heart diet is an increase in carbohydrate and dietary fibre intake. The style of eating has been shown in general population studies to be beneficial for cardiovascular profile (Schaefer et al 1981; Anderson et al 1991). In the present study, carbohydrate intake as a percentage of energy was low at a mean 41.5 per cent. This was significantly less than the recommended 55 to 60 per cent contribution to energy ($p<0.01$). Total daily fibre intake on the other hand was high and met the desired intake of 25 to 30 grams daily. This unusual dietary pattern is possibly the result of a high total energy intake, which may explain the high fibre yet low percentage energy contribution from carbohydrates. It could be assumed therefore, that a considerable proportion of transplant recipients were following dietary recommendations for increasing fibre intake.

Overall, the results of this analysis suggest that the diets of a considerable proportion of transplant recipients exceed current recommendations for total fat, saturated fat and sodium. Dietary fibre intake tends to be high, whilst carbohydrate and alcohol intakes are

on the whole, low. Before making any conclusions regarding the adherence with healthy heart recommendations in this population, however, the limitations of the chosen dietary assessment methodology must be considered. The diet history, like other techniques has several limitations in dietary assessment. Although it provides a good indication of usual intake it may neglect infrequently consumed food, inaccurately estimate or over-report intake (Thompson and Byers 1994). Thus any results must be interpreted with care.

Although the underlying aetiology of post-transplant CAD is not necessarily diet related and the role of dietary intervention has yet to be proven in improving the cardiovascular profile of cardiac transplant recipients, promoting a diet which corresponds with a healthy heart pattern of eating is a safe means of promoting sound nutritional health whilst possibly achieving cardiovascular benefits. Although the diets of the heart transplant population more comparable with healthy heart guidelines than intakes reported in the general population, considering the predisposition to cardiovascular complications in transplant recipients, adherence with recommendations is vital. Thus cardiac transplant recipients who presently only receive immediate post-transplant dietary intervention may benefit from appropriate nutrition education and counselling extending beyond the initial post-transplant period.

6. CONCLUSION

The findings of this study suggest that the St. Vincent's Hospital heart transplant population have a high risk profile for the development of cardiovascular complications including post-transplant CAD. Although the development of these risk factors appears highly related to the metabolic consequences of immunosuppressive therapy and other factors unique to transplant recipients, there is some evidence that these risk factors are modifiable with appropriate preventative and treatment protocols.

Hyperlipidaemia was a post-transplant cardiovascular risk factor which developed in this study population. At three months post-transplant, total blood cholesterol increased significantly from pre-transplant values and by 12 months post-transplant, 41 per cent of recipients were hyperlipidaemic. Although the prevalence and degree of this disorder was less than previously reported by other researchers, the combined effect of lipid elevations with immunological factors has the potential to influence CAD development.

Overweight was possibly the most significant cardiovascular risk factor evident in the post-cardiac transplant population. Immediately following transplantation, body weight decreased in these patients. Ensuing this, weight increased progressively over time and significant gains were apparent at measurement interval. Measures of body fat distribution indicated a disposition towards abdominal obesity. Corresponding increases in appetite and low levels of physical activity were demonstrated in this population. Consequently, obesity may be significant not only in its independent effects on cardiovascular health but via its influence on the establishment of other risk factors including hypertension, diabetes mellitus and hyperlipidaemia. Thus it is possible that ameriolation of weight gain may be one of the most important CAD preventative measures.

Diabetes mellitus was also evident in a small number of transplant recipients. The prevalence for this disorder being 19 per cent at 12 months post-transplant. However, it is possible that because of the presently inadequate blood glucose monitoring of these patients the prevalence of diabetes mellitus is much higher. It is likely that the combined effect of steroids and weight gain contributed to this disorder which has negative implications for cardiovascular profile.

Hypertension was one of the most prevalent of all cardiovascular risk factors in this population affecting 73 per cent of transplant recipients. Analysis of blood pressure measurements however indicated that this disorder was well controlled in the transplant population. Hence the cardiovascular risk posed by this disorder is minimised.

Comparison of the usual dietary intake of the cardiac transplant population with current healthy heart recommendations suggests that long-term adherence to dietary advice is sub-optimal in a considerable proportion of transplant recipients. Intakes of fat, saturated fat and sodium were generally greater than recommended, whilst carbohydrate intake was lower than desirable. Alcohol and cholesterol intakes on the other hand were within currently recommended levels.

Overall, the evidence from this study suggests that the potential exists for improving the cardiovascular profile of long-term cardiac transplant recipients. With monitoring and appropriate intervention it is hypothesised that the development of CAD in this population could be delayed or even reduced. However, further studies incorporating larger samples of transplant recipients are required to substantiate this.

7. RECOMMENDATIONS

On the basis of the findings of this study it is recommended that:

1. Blood lipid levels including both triglycerides and total cholesterol be regularly monitored in the post-transplant period. Transplant recipients who display undesirable lipid profiles which compromise cardiovascular health should be targeted for appropriate pharmacological, dietary or lifestyle intervention. Information regarding lipid subfractions, particularly LDL nad HDL cholesterol would also be beneficial in patient monitoring, however the cost effectiveness of such an approach needs to be considered.

2. Weight gain in post-cardiac transplant patients be monitored at regular intervals and appropriate interventions implemented. A multi-disciplinary approach to the weight control issue should be encouraged. Medical and nursing staff who have regular contact with transplant recipients should identify inappropriate weight gain and target patients for intervention. Ideally, this would include referral to a clinical nutritionist and other allied health staff who are involved with lifestyle intervention (eg. physiotherapist, psychologist). The most appropriate intervention would consider all factors relevant to post-transplant weight gain (eg. appetite, quality of life, physical activity) and be individualised to meet the patients requirements. Group education may also be effective as the group dynamics for this small population of patients is likely to be positive.

3. Waist-to-hip ratio be routinely measured as an assessment of cardiovascular risk. This would be particularly important in this population who are susceptible to increased central or android adiposity as a consequence of steroid administration. In such routine measurements, standard sites and acceptable cut-off ratios should be pre-determined.

4. Blood glucose levels be monitored at regular intervals following cardiac transplantation. This would allow for early identification of diabetes mellitus and suitable medical and nutritional intervention. In turn, this may act to delay the progression of complications (including CAD) through the establishment of good blood glucose control.

5. Blood pressure continue to be monitored to the present level and interventions to control hypertension implemented in the early post-transplant period.

6. Transplant recipients receive long term dietary follow-up from a clinical nutritionist. Healthy heart dietary guidelines should be reinforced with the aim of achieving acceptable lipid, weight and blood pressure profiles. The most effective intervention should incorporate practical aspects of improving dietary intake and focus on what foods are appropriate for consumption rather that those which are not.

7. Exercise be encouraged in this population both for cardiovascular benefits and weight control. This should include the currently recommended minimum of 30 minutes at least three times per week.

8. LIMITATIONS

The present study was limited by:

1. Small sample size

Due to time and resource constraints, only 27 cardiac transplant recipients could be included in the present study. Had a larger sample size been included, the significance these findings may have been stronger.

2. Missing Data

As information was obtained from pre-existing medical records, data collection was limited by information not recorded in medical records. This was particularly the case with blood lipid analysis.

3. Dietary intake methodology

The diet history method used to collect dietary intake data in this study is subject to inaccuracies, related to the large subjective component of this method, the reliance on participant memory and the degree of estimation involved with this technique. As a result, this dietary information gathered in this study may have been subject to over or underestimation.

4. Accuracy of retrospective data

Body weight was measured by a variety of different hospital staff and to differing degrees of precision. As a result, measurements of weight in the present study are subject to potential inaccuracies.

For a diagnosis of hypertension, blood pressure elevations are required over three consecutive readings. However, because blood pressure was retrospectively analysed

from medical records only one reading for each time period was available in this study. Hence, the actual blood pressure of participants may have differed from recorded readings.

5. Failure to examine all cardiovascular risk factors

Other cardiovascular risk factors (eg. smoking) were not examined in the present study. Hence the existence of multiple risk factors could not be adequately determined in this study.

9. AREAS FOR FURTHER INVESTIGATION:

Since heart transplantation is a relatively *new* procedure and the long-term complications are only just being recognised, there are at present many areas for investigation which have yet to be fully examined in the literature. These include:

1. The effectiveness of dietary intervention in preventing cardiovascular complications such as CAD. (eg. the effectiveness of a low fat diet in reducing hyperlipidaemia, reducing sodium intake to control blood pressure etc.) A number of studies have included diet as a component of the overall investigation however, to date, large controlled studies in this area are absent. Such a study would provide evidence as to whether more stringent healthy heart recommendations need to be developed for the cardiac transplant population.

2. The most effective means of achieving sustained weight control in this population. Excessive weight gain has multiple implications for the long term health of transplant recipients. To date, there is little information regarding the most effective way to alleviate this clinical problem.

3. The relationship between cardiovascular risk factors and the development of CAD. Although this has been previously reported in the literature, conclusions regarding the role of the different risk factors in the establishment of CAD remains controversial. Further research is needed to elucidate contributing factors.

4. The prevalence of diabetes mellitus in this population, risk factors for the development of this disorder and blood glucose control. To date in the literature, little has been reported on post-transplant diabetes mellitus. This could not be thoroughly examined in this study, due to infrequent monitoring of blood glucose levels.

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11.1 Project Approval Information

11.2 Letter to Cardiac Transplant Patients

9th August 1995

Dear

I am writing to ask you to take part in a study to help prevent long term health problems in heart transplant patients. It is being conducted by Clinical Nutritionists at St. Vincent's Hospital, in conjunction with a student from the University of Wollongong.

As a heart transplant recipient, the information that you provide could help us to understand more about the incidence of heart disease and risk factors such as high blood cholesterol, overweight and diabetes in heart transplant patients.

In turn, it may help to improve the nutrition services provided to heart transplant patients such as yourself.

To gather this information, we are contacting a group of people who have received heart transplants at St. Vincent's Hospital, Sydney. You are one of those people and we would great;ly appreciate your help with this study which involves:

❑ Measuring your weight and height
❑ Measuring your waist and hips with a tape measure
❑ You telling us about your usual diet and appetite
❑ Obtaining information form St. Vincent's Hospital medical records about your cholesterol levels, triglyceride levels, body weight and blood sugar levels
❑ Obtaining information regarding your age, medications and diagnosis from St. Vincent's Hospital medical records

For us to collect this information, we will contact you to arrange an appointment here at St. Vincent's Hospital or an alternative venue if more convenient. The appointment will be for approximately one hour between August and October 1995.

If you agree to participate, your identity will not be revealed and all information will be treated with the strictest confidence. If you decide not to take part or withdraw from the study, this will in no way affect the services provided to you by St. Vincent's Hospital.

In the strong hope that you will participate, I will be contacting you by telephone with the next few weeks.

In the mean time, if you have any questions or queries, feel free to contact Melinda Morrison or Clare Rawcliffe at St. Vincent's Hospital on (02) 361 2552.

Thank you, in anticipation of your help.

Yours Sincerely

Melinda Morrison
Student
Department of Public Health and Nutrition
University of Wollongong

Clare Rawcliffe
Clinical Nutritionist
St. Vincent's Hospital

11.3 Standard Consent Form

CONSENT FORM

ST. VINCENT'S HOSPITAL / UNIVERSITY OF WOLLONGONG FORM FOR RESEARCH STUDIES

Project Title:
The cardiovascular profile and dietary intake of post-cardiac transplant patients

Investigators:

Di Cheah
BSc (Nutrition/Biology), MDAA, SRD (UK)
Deputy In Charge, Nutrition Services
St. Vincent's Hospital

Melinda Morrison
BSc (Nutrition)
Student (Master of Science (Nutrition & Dietetics))
University of Wollongong

Clare Rawcliffe
Dip. Home Science, MDAA
Clinical Nutritionist, Cardiopulmonary Transplant Unit
St. Vincent's Hospital

Boris Gazibarich
BSc, Grad. Dip Diet MCom
Lecturer and Academic Supervisor
University of Wollongong

Contact person:
Melinda Morrison
(042) 94 1819

Di Cheah
(02) 361 2554

1. You are invited to participate in the experiment described below which is being conducted as a part of the Master of Science in Nutrition and Dietetics degree at the University of Wollongong .

2. **Background to experiment**

Heart disease is the most frequently observed long term complication of heart transplantation. Risk factors for heart disease include obesity (particularly abdominal), high blood pressure, high cholesterol and triglyceride levels and a diet high in fat, salt and low in dietary fibre.

The aim of this study is to find out more about the occurrence of these risk factors for heart disease in heart transplant recipients from St. Vincent's Hospital, Sydney.

Forty heart transplant recipients from St. Vincent's Hospital have been selected to participate in this study. These participants must be over the age of eighteen, have received a heart transplant within the past twelve to twenty-four months and have no other medical conditions (eg. cancer, kidney disease, liver disease or pancreatic disease).

It is hoped that this study will assist the Department of Nutrition Services in identifying areas which require further dietary intervention.

3. **Description of Experiment - methods and demands**

The study involves :

- ❑ Obtaining information from hospital medical records including: cholesterol levels, triglyceride levels, body weight, initial diagnosis, sex, age and current medications
- ❑ An interview to obtain information regarding your *usual* dietary intake
- ❑ Measuring body weight and height
- ❑ Taking waist and hip measurements using a tape measure

It is expected that the study will take approximately one hour.

All of the information obtained in this study will be recorded in writing and stored at St. Vincent's Hospital. Only the researchers will have access to this information and it will not be used for reasons other than those intended in

the research. The data will be analysed and may be published in a medical or nutrition journal. Participants identities will not be revealed in any published results.

4. I acknowledge that I have read the above statement which explains the nature and object and the possible risks of the investigation, and the statement has been explained to me to my satisfaction. Before signing this document I have been given the opportunity to ask questions relating to any possible physical and mental harm I might suffer as a result of my participation and I have received satisfactory answers. I have also been informed that I may not receive any benefits from participating in this study.

5. My decision whether or not to participate will not prejudice my future relations with St. Vincent's Hospital and the University of Wollongong. If I decide to participate, I am free to withdraw my consent and to discontinue participation at any time without prejudice.

6. I agree that research data gathered from the results of the study may be published provided my name is not used.

_____ _____

DATE Signature of Patient or Authorised Representative

7. I have fully explained to the patient _____ the nature and purpose of the program and the procedures to be employed as described above and such risks as are involved in their performance.

_____ _____

DATE Signature of Responsible Investigator

8. The foregoing is an accurate summary of the explanation which was made to the patient/volunteer, and the undersigned witnessed the signatures.

_____ _____

DATE Signature of Auditor-Witness

NB. If you have enquires regarding the conduct of the research, please contact The Secretary of the University of Wollongong Human Research Ethics Committee on (042) 213079

11.4 Data Collection Sheets

DATA COLLECTION SHEET

Participant Identification No.:
Date:
Sex:
DOB:
Date Transplant:
Initial Diagnosis:

Medications:
❑ HT_____ ❑ CHOL _____ ❑ DM _____

Biochemistry:

Month	T.Cho	BSL's	TG's	B.P.	Wt.	BMI
0						
1						
3						
6						
12						
18						
24						

Anthropometry
Weight (kg): Height (cm): BMI:

Waist (cm): #1: #2:
Hips (cm): #1: #2:
WHR:

FOOD FREQUENCY CHECKLIST

How many times each day / week would you eat the following foods:

✓	Food	Daily	Weekly	Type
	Bread			
	Breakfast Cereal			
	Pasta / Noodles			
	Rice			
	Fruit			
	Green Vege			
	Orange Vege			
	White Vege			
	Milk			
	Cheese			
	Yoghurt			
	Cream / Sour Cream			
	Eggs			
	Red Meat			
	Chicken			
	Fish			
	Processed Meats			
	Cakes			
	Biscuits			
	Chocolates			
	Confectionary			
	Nuts			
	Crisps / Snack Foods			
	Ice Cream			
	Soft Drinks			
	Cordials			
	Alcohol			
	Mayonnaise / sauces / gravies			
	Salt			
	Pepper			

Food Preparation Data

What kind of butter / margarine do you use?_____
What kind of oil do you fry in?_____
What cuts of meat do you most commonly use?_____
Do you eat the fat on meat?_____
How do you prepare your meat / fish / chicken?_____
How do you prepare your vegetables?_____
What kinds of ready made / processed foods do you eat?_____
Do you eat out or have take away's? How often?_____
Have you seen a dietitian before?_____
Are you presently following any kind of special diet? If yes, what kind?_____

How would you describe your appetite at present?
POOR GOOD EXCELLENT
Have you noticed any changes in your appetite since your transplant?
INCREASED DECREASED NO CHANGE
Have you noticed any changes in your weight since your transplant?
INCREASED DECREASED NO CHANGE
Do you participate in any regular exercise? If yes, what and how often?

_____

11.5 National Heart Foundation Standards for Alcohol Risk

Risk Levels

Category	Description	Males	Females
A	Non-drinkers		
B	Average intake less 3 drinks	None	Low
C	Average intake of 4 drinks or 9-12 drinks in any day	Low	Intermediate
D	Average intake of 5-8 drinks or occasional excess	Intermediate	High
E	Average intake of 9-12 drinks or frequent or great occasional excess intake	High	Very High
F	Average daily intake over 12 drinks	Very High	Very High

	Amount: No. of drinks					
Frequency of Drinking	**1-2**	**3-4**	**5-8**	**9-12**	**13-20**	**> 20**
Less than once week	B	B	B	C	D	E
1 or 2 days	B	B	B	C	D	E
3 or 4 days	B	B	C	D	E	F
5 or 6 days	B	C	D	E	F	F
Every day	B	C	D	E	F	F

11.6 Raw Data

			MONTH				
Pt.	Pre-op	1	3	6	12	18	24
1	3.4	7.9	5.4	5.6			
2	5			7.3		6	
3				6.8	5.1	4.7	4.8
4	4.8			5.54			
5	3.9		5.5	6.5	5.3	6	
6	5.6	4.9	5.6	5.5	5.3		
7	4			4.7	4.7	3.5	4.7
8	4.6		5.9	6	6.3	6.8	
9	5.2		8.9	7.7	6.2	5.9	
10	7.5	5.9	5.8	6.6	5.8		
11	4.8		6	6.1	6	6.2	
12	3.4		5.2	5			
13	3.8	5.3	4.4	4.3			
14	2.9		5.8	5.2	5.4		
15	2.3	3.2	4.2	4	3.9		
16	5.9	7.5	7.4	6.7	6.9	5.9	
17	5.1	6	6.7	5.5	5.6		
18	6.3	5.7	6.2	5.3	4.4		
19	3.5	5.6		7.2	6.5		6.9
20	3.7	7.2	6.1	4.7	4.7		
21	4.8		4.4	3.9	4.5	4.3	4.9
22	5.6	6	10.6	7.8	6.6	5.8	
23	3.4		5.4	5.8	5.5	5.7	
24							
25	6.4	11.8	8.1		5.7		
26	3.1			5.2			
27	2		5.3	6.3	4.8		

1. Cholesterol Levels

			MONTH				
Pt.	**Pre-op**	**1**	**3**	**6**	**12**	**18**	**24**
1	0.7						
2	3			2.88		2.2	
3				3.8	2.8	2.5	2.3
4	1.3			0.97			
5	0.7		1.1	0.89	0.9	0.9	
6	1.4						
7	1			1.3	1.16	1.41	1.46
8	1.4		1.7	1.2	1.9	1.9	
9	2.5		3.9	3.4	2.73		
10	3.5						
11	1.7		2.8	4.1	2	2.7	
12	1		1	1			
13	1.1						
14	1.2		1.5	1	1.8		
15							
16		2.08	2.26	2.5	2.6	1.7	
17	0.7						
18	1.5						
19	1.3	1.1		1.6	1.5		
20	1.5						
21	2.9		1.6	1.4	1.7	2.2	
22	3						
23	0.9		1.02	1.1	1.2	1.5	
24							
25	1.2	1.1					
26	1.2			1.7			
27							

2. Triglyceride Levels

			MONTHS				
Pt.	**Pre-op**	**1**	**3**	**6**	**12**	**18**	**24**
1	20	20	21	23	23		
2	29	27	28	32	35		
3	25	22	24	25	27	29	
4	25	25	27	27	27		
5	19	20	21	22	23	24	
6	24	22	22	23	22		
7	21	21	21	22	21	22	23
8	27	24	29	30	31	33	
9	26	25	28	29	30	33	
10	25	24	23	23	23		
11	21	20	21	23	24	25	
12	20	20	21	22	22		
13	21	19	19	22	20		
14	26	24	27	29	31		
15	25	25	26	26	25		
16	28	29	30	30	34	33	
17	28	27	26	27	28		
18	26	25	26	27	27		
19	22	20	20	24	25	25	24
20	22	23	23	23	24		
21	26	24	25	28	32	33	33
22	29	28	29	28	27		
23	25	25	28	29	31	36	
24	27	25	27	27	28		
25	28	29	30	31	33	33	
26	32	34	33	34	37	43	
27	22	20	22	23	23	23	

3. Body Mass Index

			NUTRIENT							
	Energy	Total Fat	Saturated Fat	Mono Fat	Poly Fat	Protein	Carbohydrate	Fibre	Sodium	Cholesterol
	Kilojoules	*Grams*	*Grams*	*Grams*	*Grams*	*Grams*	*Grams*	*Grams*	*mmol*	*Milligrams*
Pt.										
1	8706.3	83.7	24.9	37.4	10.5	133.6	199.1	31.7	118.5	388.2
2	9636.3	68.9	28.2	24.6	8.8	126.2	297	27.7	150.6	359
3	7940.5	67.5	27.3	22.8	11.7	99	227.8	26.5	85.5	239
4	7801	54.4	23.7	18.7	7.4	107.9	239.4	29.4	188.2	223.4
5	11344.6	100.1	25.5	36.3	30.2	151.1	277.1	32.4	113.1	321.4
6	14260	146.1	52.9	61.3	17.9	219.7	330	30.9	132.8	605.4
7	13968	116.8	43.5	44.7	13.8	130.7	409.2	38	158	297
8	6724	50.9	13.1	21	10.6	101.5	127.4	28.8	70	249.2
9	7947.1	63	16.7	31.1	15.2	112.6	208.8	33.7	157.7	166.6
10	10526	80.2	30.9	27.7	14.7	125.8	273.4	21.3	111	358
11	7742	62.9	20.1	22	14.7	98.1	219.8	21.9	140.5	256
12	6892	44.4	18.3	16.1	4.8	95	213.1	21.5	95.1	198.4
13	12149.9	128.1	64.2	44.8	18.9	144	291.5	29.8	132.8	436.9
14	13273	118	29.9	56.2	18.7	154.9	287.3	56.1	142.2	346.5
15	14471.2	149.7	52.8	53.8	31.9	118.3	406.6	29.1	214.9	280
16	8152	71.4	30	27.4	6.8	133.7	151.3	27.1	61.8	284.4
17	10806	107.5	40.4	43.6	13.7	134.7	210.2	24.3	84	296.5
18	11247	69	22.8	21.5	11.2	144.6	373.3	63.8	117	207
19	15673	172.8	60.1	76.7	17.1	278.8	259.9	31	72.6	879
20	10640	99.3	31.9	34.2	26.1	131.8	228.6	19.7	140.7	493.6
21	7538	63.4	20.9	27.6	8.1	72.9	185.3	30.8	83.2	134.7
22	10780	89.5	33.1	32.2	16.5	126	319.5	33.2	122	316
23	9280	77.2	23.6	35	12.3	111	220.3	20.8	112	192.4
24	12685.5	117.5	58.6	39.5	9	134.5	347.7	32.3	111.9	249.9
25	7930.8	60.6	15.4	23.1	17.1	78.2	258.8	35.7	71.1	122.8
26	13229.7	128.7	50.7	48	30	117	297.1	220.1	113	316
27	10763.5	74.9	21.6	22.2	23	165.2	299.1	54.5	134.2	326.7

4. Nutrient Intakes

MALE			
Pt.	**Mean Waist**	**Mean Hip**	**WHR**
1	110	107	1.03
2	84.5	88	0.96
3	117	119	0.98
4	93	97	0.95
5	124.5	108	1.15
6	94	95	0.989
7	86	90	0.95
8	84	91	0.92
9	113	103	1.09
10	93.5	97	0.96
11	110	108	1.02
12	85	89.5	0.94
13	119	113	1.03
14	114	104	1.09
15	85	89	0.96
16	89	93	0.96
17	91.5	89	1.02
18	97.5	93	1.05
19	91	87	1.04
20	126.5	119	1.06
21	94	94	1
22	132.5	120	1.1
23	91.5	90	1.02
FEMALE			
24	128	143.5	0.89
25	87	116	0.75
26	89	116	0.77
27	89	111	0.8

5. Waist / Hip Measurements